Dynamics of Oliveros Virus Infection in Rodents in Central Argentina

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ABSTRACT

Oliveros virus (OLV) is an arenavirus hosted by the sigmodontine rodent, *Necromys benefactus*, in central Argentina. We report a 3-year longitudinal field study of the dynamics of OLV infection in host populations from 15 localities in two provinces on the central Argentine pampa. There was an overall 3-year period immunofluorescent antibody prevalence of 25% in the host population, and infected hosts were found throughout the study area. Spill-over infection into common sympatric species was rare. Infection dynamics exhibited many of the patterns seen for other rodent-borne arenaviruses and hantaviruses, but had some unique characteristics. Host population density was highest in autumn and lowest in spring, while antibody prevalence was highest in spring and lowest in autumn. Virus transmission was horizontal: infection was strongly associated with age, reaching 45% prevalence in the oldest individuals, and prevalence of infection was equal among male and female hosts. Infection may have been associated with scars, which were also approximately equally distributed among male and female *Necromys*. **Key Words:** Epidemiology—Field studies—Rodent-borne—Zoonotic. Vector-Borne Zoonotic Dis. 7, 315–323.

INTRODUCTION

THE ARENAVIRUSES (family *Arenaviridae*) are a group of rodent-borne RNA viruses that are the etiologic agents of several severe zoonotic diseases in humans (Enria et al. 2006). All known arenaviruses are hosted by rodents of the family Muridae, with one possible exception—Tacaribe virus has been associated with bats of the genus *Artibeus* (Downs et al. 1963). The Old World arenaviruses lymphocytic choriomeningitis virus (LCMV) and Lassa virus cause lymphocytic choriomeningitis and Lassa fever, respectively. The New World or Tacaribe complex arenaviruses cause the South American hemorrhagic fevers (Argentine, Bolivian, Venezuelan, and Sabiá [Brazilian] hemorrhagic fevers). Effective prevention or management of zoonotic diseases requires an in-depth knowledge of the ecology and epizootiology of the zoonotic pathogen in nature (Mills and Childs 1998). Nevertheless, ecological studies of the South American arenaviruses in their natural host populations are rare. Perhaps because of the relative remoteness and scarcity of resources in the disease endemic areas for the arenaviral hemorrhagic fevers, the ecology of only a few arenaviruses has been

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studied in any detail (Demby et al. 2001, Enria et al. 2006).

Oliveros virus (OLV) (Mills et al. 1996) is an arenavirus of the New World Tacaribe Complex that is hosted by the sigmodontine rodent, *Necromys benefactus* (formerly *Bolomys obscurus*) (Massoia and Pardiñas 1993, Wilson and Reeder 2005). OLV was serendipitously discovered in central Argentina while conducting ecological studies of rodent hosts of Junín virus (JUNV), an arenavirus that is the etiologic agent of Argentine hemorrhagic fever (AHF) (Mills et al. 1994, 1991a). The prototype strain of OLV has been fully characterized and sequenced (Bowen et al. 1996, Mills et al. 1996). Two additional isolates of OLV from the same host species were identified by plaque reduction neutralization tests (Mills et al. 1996), and a strain originally designated "Pampa virus" (Lozano et al. 1997), also isolated from *N. benefactus* later was shown to be OLV (Bowen et al. 2000). The ecological and epizootiological studies of JUNV provided a large bank of rodent sera and tissues, as well as ecological data on rodent species collected in and near the AHF endemic area, an area that included portions of four provinces in central Argentina (Fig. 1). Retrospective analysis of these stored sera and accompanying ecological data have provided details concerning the dynamics of the

Necromys-Oliveros, host-virus relationship. Although OLV has not been recognized as a human pathogen, it is one of few arenavirus and host systems to be subject to a long-term mark-recapture study in its natural habitat. Herein we take advantage of the availability of the large bank of rodent sera and ecological data to provide the first longitudinal study of OLV dynamics in its natural host population on the central Argentine Pampa. We describe the prevalence and ecological correlates of infection by OLV in host populations.

METHODS

Description of the sampling area

Small mammal trapping was conducted at 15 localities in and near the AHF endemic area. This area, which currently has a human population of over 5 million and comprises over 150,000 square kilometers on the central Argentine pampa (Enria et al. 2006), is a rich agricultural zone including northern Buenos Aires, southern Santa Fe, southeastern Cordoba, and extreme-northeastern La Pampa provinces (Fig. 1). The habitat consists primarily of cattle pastures and crop fields (primarily corn, soybeans, and wheat), separated by more stable,
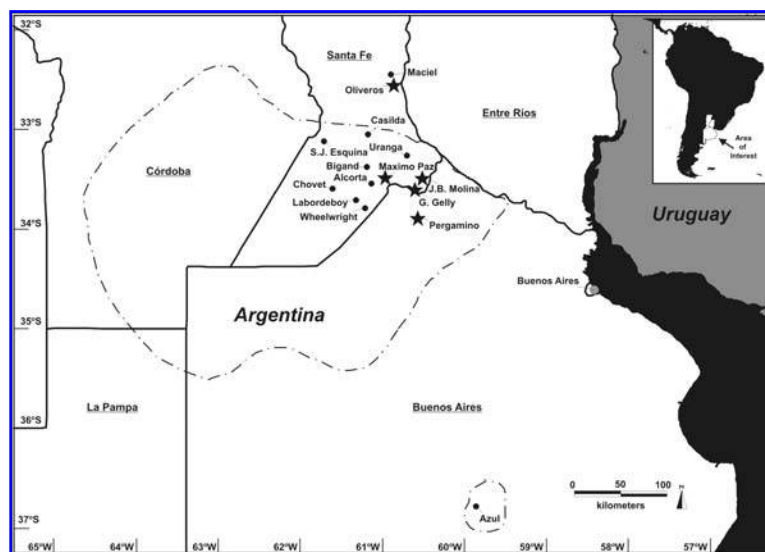

FIG. 1. Location of 15 rodent sampling sites within and near the Argentine hemorrhagic fever endemic area (dashed line; including disjunct area around city of Azul), October 1987 to August 1990. Stars represent sites where longitudinal mark-recapture grids were located.

weedy borders, including roadsides, fence lines, and railroad rights-of-way.

Rodent trapping and sampling

Detailed descriptions of rodent trapping and processing have been published (Mills et al. 1991a, 1992). Briefly, samples were collected from rodents captured during two overlapping studies. In the first study, between October 1987 and August 1990, rodents were trapped on farms at 15 localities across the AHF endemic area (Fig. 1) using Sherman and Tomahawk live-capture traps. Captured rodents were euthanized, and blood and tissue samples were collected for serological and virological analyses. The second study involved sampling rodents captured on seven long-term mark-recapture grids at five of the 15 sites (Fig. 1, stars). The mark-recapture grids were operated for three consecutive nights at 5-week intervals between March 1988 and August 1990. Captured rodents were anesthetized before taking a blood sample from the retro-orbital capillary sinus. They were then weighed, measured, affixed with a uniquely numbered ear tag, and released at the site of capture on the trapping grid.

Serology

Samples of the six most commonly captured small mammals (*N. benefactus, Mus musculus, Akodon azarae, C. musculinus, C. laucha,* and *Oligoryzomys flavescens*) were tested for antibody to OLV by immunofluorescent antibody test (IFAT). Ten-well spot slides were coated with a suspension of African green monkey kidney epithelial (Vero) cells infected with OLV (prototype strain RIID 3329) (Mills et al. 1996) using standard techniques (Jahrling 1992). Twenty microliters of each test serum diluted 1:10 in phosphate-buffered saline (PBS) were added to spots in duplicate and allowed to incubate for 30 min at room temperature. Binding of specific antibody was detected using fluorescein isothiocyanate-conjugated goat anti-hamster IgG (Sigma, St. Louis, MO). Serum from guinea pigs inoculated with OLV strain RIID 3229 was used as a positive control. Previous studies have indicated that the anti-hamster IgG conjugate detects specific anti-body in all of the common sigmodontine rodents from central Argentina (Mills et al. 1994, 1996). Slides were examined under a fluorescence microscope and samples demonstrating specific fluorescence (bright green granular fluorescence in the cytoplasm) were scored as ±, +1, +2, +3, or +4. Fluorescence of +1 or stronger was considered positive. Sera were initially screened at a 1:10 dilution in PBS. Antibody-positive sera were titered at fourfold dilutions from 1:40 to 1:10,240. Titers are presented as the reciprocal of the highest dilution exhibiting specific cytoplasmic fluorescence. OLV antibody-positive sera were checked for cross-reactivity to LCMV and JUNV antigens (the only other recognized arenaviruses in the area). LCMV and JUNV spot slides were prepared using the Candid I (vaccine) strain of JUNV and the Armstrong strain of LCMV.

All available serum samples from *N. benefactus* and subsamples of approximately 100 each of the other five common rodent species were tested. So that the subsamples were representative of the entire sampling area, we selected these non-*Necromys* samples approximately equally from all sampling sites from which samples were available.

Data analysis

All captured *N. benefactus* were categorized into four mass classes on the basis of body weight at time of capture. The recorded weight distribution for all captured individuals was divided into quartiles as follows: mass class I ($\leq$22.9 g); II (23.0–27.8 g); III (27.9–34 g); and IV ($\geq$34.1 g). Trap success (number of captures per 100 trap nights, expressed as a percent) was used as an estimate of rodent relative population density. Data from the mark-recapture grids were used to calculate incidence using the person-time denominator method (Mausner and Kramer 1985) according to the following formula: sum of individual mouse seroconversions/sum of mouse-months of observation of the at-risk population. Mice found antibody-positive that were antibody-negative on the previous capture were considered to have undergone seroconversion. Mouse-months were defined as the sum of all the intervals between successive captures when mice remained antibody negative plus half of the

TABLE 1. PREVALENCE OF IMMUNOFLUORESCENT ANTIBODY TO OLIVEROS VIRUS IN *NECROMYS BENEFACTUS* CAPTURED FROM FARMS AT 15 LOCALITIES IN CENTRAL ARGENTINA

Locality	No. positive/tested[a]	Positive, %
Maciel	4/5	80
Oliveros	18/45	40
Casilda	2/5	40
Chovet	5/15	33
Bigand	8/26	31
General Gelly	9/34	26
J.B. Molina	14/53	26
Labordeboy	1/4	25
Wheelwright	4/16	25
Pergamino	20/80	25
Maximo Paz	7/54	13
Uranga	5/39	13
Alcorta	1/11	9
S.J. Esquina	0/5	0
Azul	0/1	0
Total	98/393	25

[a]Represents numbers of individual mice.

interval when seroconversion occurred (Childs et al. 1987, Mills et al. 1992). Monthly prevalence was calculated by dividing the number of antibody-positive individual mice by the number of individual mice tested in a given month.

Statistical analysis

Data were analyzed using SPSS statistical software.

RESULTS

During 34 months of trapping, 8,426 individual animals of 15 species were captured 10,327 times. Six species of rodents (*C. laucha, C. musculinus, A. azarae, O. flavescens, N. benefactus,* and *M. musculus*) comprised 98% of captures. The nine remaining small-mammal species were captured at frequencies of ≤0.5%. Mark-recapture grids and removal traplines accounted for 57.2% and 42.8% of total captures, respectively. Of 585 individual *N. benefactus* captured, 67% (*n* = 393) were available for IFA testing, which included 411 test specimens because a few were animals captured and sampled on mark-recapture grids during more than one trapping occasion.

Twenty-five percent of tested individual *N. benefactus* had antibody reactive with OLV anti-

gen (Tables 1 and 2). Antibody-positive animals were distributed across the sampling area and were found at all sites where more than five animals were captured and tested. At sites where antibody-positive *Necromys* were found, prevalences varied from 9% to 80% (Table 1). Only three of 13 sites with antibody-positive *Necromys* had prevalences below 25%. A small percentage (1–6%) of three other common rodent species had detectable OLV antibody (Table 2).

Antibody-positive *Necromys* were found throughout the year. Prevalence tended to peak in the austral spring, when overall densities were near their nadir; prevalences were lowest in autumn, when densities were generally highest (Fig. 2).

Of the 97 *Necromys* sera that were tested and titered to endpoint for all three antigens (Table 3), 54 were reactive only with OLV virus. When cross-reactivity was observed (Table 4), the titer to OLV was higher (usually at least eightfold higher) than for JUNV or LCMV except in three cases. In two of the three cases, the JUNV titer was 4- and 16-fold higher than the OLV titer, and in one case, the JUNV titer was equal to the OLV titer. LCMV cross reactivity was weak; titers never exceeded 160 and were always at least 16-fold lower than the OLV titer.

For the two *Akodon* that had OLV-reactive antibody, the OLV titer was only 40, and there was no reactivity with either JUNV or LCMV. Seven *Mus* had antibody reactive to OLV (Table 5). Four of these had higher titers to LCMV; one had the highest titer to JUNV, one had a low titer to OLV only, and one had low titer to both OLV and LCMV.

TABLE 2. PREVALENCE OF IMMUNOFLUORESCENT ANTIBODY TO OLIVEROS VIRUS IN SIX COMMON RODENT SPECIES CAPTURED IN CENTRAL ARGENTINA

Species	No. positive/no. tested[a] (%)
Necromys benefactus	98/393 (25%)
Calomys musculinus	1/117 (1%)
Calomys laucha	0/110
Akodon azarae	2/107 (2%)
Mus musculus	7/118 (6%)
Oligoryzomys flavescens	0/109
Total	112/971 (12%)

[a]Represents numbers of individual mice.
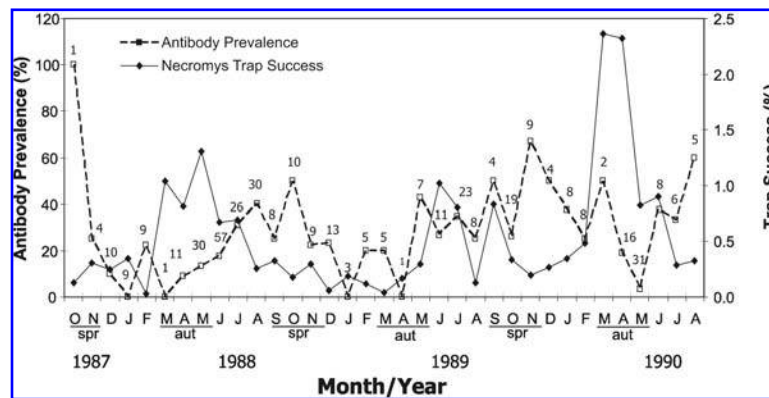Taxonomy follows Wilson and Reeder (2005).

FIG. 2. Monthly relative population density (trap success; solid line) and prevalence of antibody to Oliveros virus (dashed line) in populations of *Necromys benefactus* at 15 sites on the central Argentine pampa, October 1987 to August 1990. Numbers above data points represent numbers of samples tested. Spr, spring; aut, autumn.

Characteristics of infected mice

Antibody to Oliveros virus was distributed approximately equally between male (58/227 = 26%) and female (42/178 = 24%) mice. Antibody prevalence increased with mass: 8/99 = 8% in mass class I, 17/101 = 17% in mass class II, 28/102 = 27% in mass class III, and 46/102 = 45% in the largest (oldest) adults (mass class IV; chi square for linear trend = 40.25, $p < 0.00001$).

Approximately equal overall proportions of males (10.6%) and females (8.4%) had visible scars and these proportions increased by mass class for both genders. Approximately twice as many mice with antibody had scars (16%) as did mice without antibody (7.5%). However, because both wounding and infection status are associated with age (mass) we corrected for this confounder by examining the association of scars and antibody for each mass class separately (Fig. 3). Antibody-positive mice had significantly more scars than antibody-negative mice only in mass class III, where there was a threefold difference ($p = 0.04$, Fisher's exact test).

Incidence

The incidence of OLV infection in *N. benefactus* during the 36-month study period was 21.3 infections per 100 mice per month.

DISCUSSION

This first longitudinal study of the dynamics of Oliveros virus infection in its natural host demonstrates many similarities with other rodent-borne viral agents. However, it also indicates some important differences, suggesting that the transmission of OLV in *N. benefactus* populations may follow a different pattern. The clear association of antibody prevalence with age implies that horizontal transmission is the primary mechanism of transmission, and the very low prevalence in juvenile animals suggests that vertical transmission may be absent or rare. This demonstration of horizontal transmission is concordant with patterns for some other rodent-borne viral hemorrhagic fever viruses (most all hantaviruses, and some arenaviruses such as Junín virus) (Mills et al. 1992, 1999) but contrasts with the pattern for at least

TABLE 3. NUMBERS OF OLIVEROS VIRUS ANTIBODY-POSITIVE SERA FROM *NECROMYS BENEFACTUS* THAT WERE CROSS-REACTIVE WITH TWO OTHER SYMPATRIC ARENAVIRUSES FROM CENTRAL ARGENTINA

OLV titer	OLV+	JUNV+	LCMV+	OLV only
10	13	0	0	13
40	5	0	0	5
160	18	1	1	16
640	20	5	2	14
2560	17	11	8	4
10240	24	21	16	2
Total	97	38	27	54

Column 5 presents titers for samples that were not cross-reactive (positive for OLV only). Titers are expressed as the reciprocal of the highest dilution exhibiting specific cytoplasmic fluorescence by immunofluorescent antibody test.

OLV, Oliveros virus; JUNV, Junin virus; LCMV, lymphocytic choriomeningitis virus; +, antibody-positive.

TABLE 4. ENDPOINT TITERS FOR 38 SERUM SAMPLES FROM *NECROMYS BENEFACTUS* THAT WERE REACTIVE WITH BOTH OLIVEROS (OLV) AND JUNÍN (JUNV) VIRUS ANTIGEN BY IMMUNOFLUORESCENT ANTIBODY TEST

Sample	OLV titer	JUNV titer
6286	160	10
6564	640	10
6966	640	10
6387	640	160
6594	640	640
5920	**640**	**10,240**
6690	2560	10
7741	2560	10
11,393	2560	10
6198	2560	40
6595	2560	40
6689	2560	40
6645	2560	160
7418	2560	640
7419	2560	640
2098	2560	640
2031	**2560**	**10,240**
1920	10,240	10
6521	10,240	40
6927	10,240	40
8817	10,240	160
19	10,240	640
1760	10,240	640
1893	10,240	640
4876	10,240	640
5846	10,240	640
6022	10,240	640
6172	10,240	640
6361	10,240	640
6451	10,240	640
6453	10,240	640
6481	10,240	640
6688	10,240	640
6722	10,240	640
7072	10,240	640
8922	10,240	640
7337	10,240	2560
8458	10,240	2560

Fifty-four samples had no cross-reactivity (reactive only with OLV antigen). Boldfaced samples had higher titers for JUNV than OLV and may represent virus spillover (infection of *N. benefactus* with JUNV); underlined samples had OLV titers that were equal to (in one case) or only fourfold higher than the JUNV titer (6 cases). Titers are presented as the reciprocal of the highest dilution exhibiting specific cytoplasmic fluorescence.

two Old World arenaviruses (Lassa virus and lymphocytic choriomeningitis virus), which show evidence of vertical infection (Buchmeier et al. 1980, Johnson 1981). For several rodent-borne viruses (e.g., Junín, and numerous hantaviruses) (Mills et al. 1992, 1999), male mice have a higher prevalence of wounds, which correlates with a higher prevalence of antibody,

suggesting that these viruses are transmitted via agonistic encounters, especially among the more aggressive males. However, among *N. benefactus*, males and females were equally likely to be infected with OLV and equally likely to have scars. Mice with antibody were more likely to have scars, especially among the young-adult mass class—mice that may be reaching reproductive age and dispersing. This combination of results may suggest that OLV is transmitted via aggressive encounters that result in wounding, but that females are just as likely to be involved in such encounters as males. These findings match the model described for Seoul virus transmission in Norway rats (Glass et al. 1988), where infection was associated with acquisition of scars and with the onset of sexual maturity, but was equally likely in males and females. Our inspection for scars was cursory, and most scars were observed on the tail and ears, where they were more easily detected. Doubtless, many scars had healed or were hidden under the fur and were not detected.

The alternating spring–autumn peaks in antibody prevalence and host density, respectively, are typical of the pattern observed previously for rodent-borne hemorrhagic fever viruses in temperate ecosystems (Mills et al. 1999, Niklasson et al. 1995). This delayed-density-dependent prevalence of infection may be driven by the interplay between virus transmission/antibody accumulation and recruitment of uninfected young. Because OLV is hor-

TABLE 5. IMMUNOFLUORESCENT ANTIBODY TITERS TO THREE VIRAL ANTIGENS FOR SERA COLLECTED FROM SEVEN HOUSE MICE (*MUS MUSCULUS*) COLLECTED IN CENTRAL ARGENTINA

Sample no.	OLV	JUNV	LCMV
1	2560	640	10,240
2	40	neg	10,240
3	40	neg	2560
4	40	neg	2560
5	80	neg	10
6	160	640	neg
7	40	neg	neg

Titers are presented as the reciprocal of the highest dilution exhibiting specific cytoplasmic fluorescence.
OLV, Oliveros virus; JUNV, Junín virus; LCMV, lymphocytic choriomeningitis virus; neg, negative (<10).
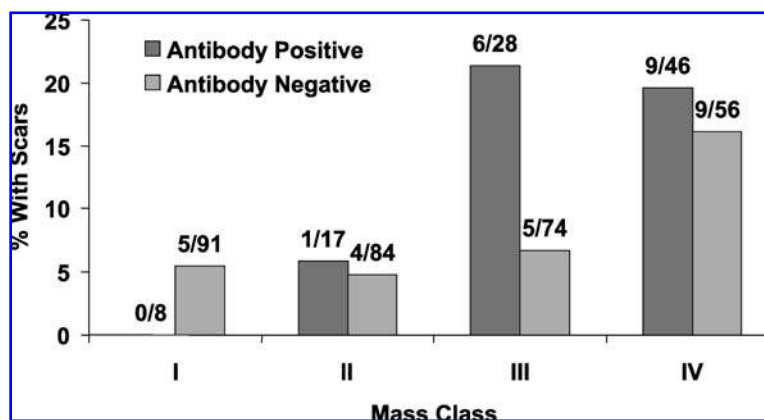
FIG. 3. Prevalence of scars in antibody-negative and antibody-positive rodents for *Necromys benefactus* captured on the central Argentine pampa, October 1987 to August 1990. Mass classes are as follows: I (≤22.9 g), II (23.0–27.8 g), III (27.9–34 g), and IV (≥34.1 g). Seven captures with missing data for mass are not included.

izontally transmitted, the recruitment of uninfected young during the spring–autumn breeding period (juvenile dilution) (Mills et al. 1999) results in a lowering of the overall antibody prevalence. After recruitment ceases in the fall, virus transmission in high-density populations and subsequent acquisition of antibody increases prevalence over winter to a spring peak, just before recruitment begins again in the spring (Mills et al. 1999).

The overall prevalence (25%) and incidence (21.3 new infections per 100 mice per month) found in the current study are high when compared to similar studies of several other rodent-borne hemorrhagic fever viruses. During a study of Junín virus infection in *Calomys musculinus* at the same sites and during the same time period as the current study, we found prevalences of infection of 3.6% (Mills et al. 1991a) to 10.9% (Mills et al. 1994). The calculated incidence rate for JUNV infection in *C. musculinus* was 11.7 new infections per 100 mice per month (Mills et al. 1992). In the United States, the prevalence of infection with Sin Nombre hantavirus in its host (*Peromyscus maniculatus*) was 2.6% (Calisher et al. 2005) to 13% (Douglass et al. 2001), and calculated incidence rates were 0.3–6.1 new infections per 100 mice per month (Calisher et al. 1999, 2005). Only one rodent-borne hantavirus (Limestone Canyon virus, hosted by *Peromyscus boylii*) was found to have a prevalence (20%) and incidence (17–34 infections per 100 mice per month) sim-

ilar to that observed in this study (Abbott et al. 1999). A Norway rat population in Baltimore, Maryland, had an even higher prevalence of infection with Seoul hantavirus (34%), but a lower incidence of infection (12.06 per 100 rats per month) (Childs et al. 1987).

We have assumed that a positive result on an IFA test for a *Necromys* serum sample represents infection with OLV. The only other arenaviruses known to occur in the sampling area are JUNV and the old world arenavirus LCMV. The relatively weak cross reactivity of *Necromys* sera with the other arenaviruses supports this assumption. With rare exceptions, cross reactivity with JUNV or LCMV was common only for those samples that were reactive at the highest OLV antibody titers. Reactivity to OLV antigen was usually eightfold or more greater than to JUNV antigen. In one case the titers were equal, and in six additional cases, the difference was only fourfold. Since a fourfold difference represents only a single dilution, a conservative approach would be to consider these six results as uninterpretable. The two cases where the JUNV titer was higher (in one case 16-fold higher) than the OLV titer may represent spillover of JUNV from its sympatric natural host (*C. musculinus*) to *N. benefactus*. As the two species sometimes share the same roadside and fenceline microhabitats virus transfer among these two species, either by direct contact or environmental contamination, would be expected. For the seven OLV-positive *Mus*, the

much higher relative titers to LCMV suggest LCMV infection in four cases. The other three cases with relatively low (40–640) or no reactivity for all 3 viruses do not suggest a simple explanation and may be artifactual.

N. benefactus is restricted to central Argentina (portions of Córdoba, La Pampa, and Buenos Aires provinces) (Wilson and Reeder 2005) and was only recently separated by taxonomists from the closely related but more widespread *N. obscurus*, which is described as an inhabitant of wet areas and grassy fields (Redford and Eisenberg 1992). Within the area of this study, *N. ben*efactus is largely restricted to the narrow linear borders of cultivated fields. While several sympatric species including *C. musculinus* and *C. laucha* take advantage of crop fields as habitat when vegetative cover is adequate, *N. benefactus* rarely was captured away from the weedy borders (Mills et al. 1991a). The relatively higher prevalence of infection in *N. benefactus* might be partially explained by this restriction of the population to small patches of habitat, resulting in more frequent encounters and virus transmission events.

The recent taxonomic separation of *N. benefactus* from *N. obscurus* raises the question of whether OLV is restricted to *N. benefactus* or whether it is shared by closely related congeners that share the lowland savanna habitats of Argentina, Uruguay, Paraguay and southern Brazil. The highly specific and apparently co-evolved relationship between arenaviruses (and hantaviruses) and their sigmodontine rodent hosts suggests the possibility of closely related viruses associated with other *Necromys* species. It is likely that a large number of arenaviruses associated with sigmodontine hosts remain to be described.

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