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SEROLOGICAL EVIDENCE OF CALIFORNIA GROUP AND CACHE VALLEY VIRUS INFECTION IN MINNESOTA WHITE-TAILED DEER

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ABSTRACT: Blood samples were obtained from 138 white-tailed deer (*Odocoileus virginianus*) harvested at three sites surrounding the greater Minneapolis–St. Paul, Minnesota, metropolitan area (USA) and tested for neutralizing antibody to Cache Valley virus and three California serogroup (Jamestown Canyon, La Crosse, trivittatus) viruses (Bunyaviridae). Deer at each site had neutralizing antibody to one or more California serogroup viruses and/or Cache Valley virus. The majority of adult deer (85%) had antibody to both a California serogroup virus and Cache Valley virus. Antibody prevalence varied significantly with age of the deer. Fawns had a significantly lower prevalence of antibody to either a California serogroup (17%) or Cache Valley virus (39%) than did older (>1-yr-old) deer (89% for a California serogroup virus and 91% for Cache Valley virus). The geometric mean titers of antibody in fawns to California serogroup (1:6) and Cache Valley viruses (1:17) were also less than that seen in older animals (1:11 and 1:28 for California serogroup and Cache Valley viruses, respectively). Of 76 older deer with antibody to the California serogroup, 91% had antibody specific for Jamestown Canyon virus. Jamestown Canyon is the primary California serogroup virus circulating in the suburban/rural Minneapolis–St. Paul area. Transmission occurs in an enzootic pattern similar to that documented in Indiana and Michigan. Cache Valley virus also appears to be enzootically transmitted in this area. However, the impact on domestic or wild animal populations is unknown.

Key words: California serogroup viruses, Bunyaviridae, Jamestown Canyon virus, Cache Valley virus, white-tailed deer, *Odocoileus virginianus* serosurvey.

INTRODUCTION

The first fatal case of La Crosse (LAC) virus encephalitis in Minnesota (Thompson et al., 1965) established the presence of California serogroup viruses in the Midwest. In subsequent case reports and serologic surveys, the enzootic and endemic occurrence of LAC and trivittatus (TVT) viruses in Minnesota was established (Monath et al., 1970; Calisher, 1983; Hurwitz et al., 1983). Jamestown Canyon (JC) virus is a human neuropathogen (Grimstad et al., 1982), is enzootic in virtually all of temperate North America (Grimstad, 1988) and is endemic in parts of the upper Midwest (Grimstad et al., 1986).

Cache Valley (CV) virus was first isolated from *Culiseta inornata* mosquitoes in Utah (Holden and Hess, 1959) and subsequently from multiple mosquito species in Minnesota (Calisher et al., 1986). There have been no confirmed reports of illness in humans or other vertebrates attributed to CV virus in Minnesota. However, recent work suggests that CV virus may play an important role in disease etiology among domestic animals elsewhere, and that its importance as an etiologic agent must be reassessed (C. H. Calisher, pers. comm.). Its association with wildlife diseases remains to be established.

Serum antibody prevalence rates to JC virus in free-ranging yearling and adult white-tailed deer (*Odocoileus virginianus*) populations in Indiana, Michigan and in suburban areas of Chicago, Illinois (USA), often exceed 80%; rates in the fawn cohort rarely approach 15 to 20% (Boromisa and Grimstad, 1987; P. R. Grimstad, unpubl. data). Recent evidence of widespread exposure to California serogroup viruses, particularly JC, in midwestern deer populations, and concern for the possible involvement of CV virus in animal disease prompted the current survey for serologic evidence of these viruses in Minnesota white-tailed deer.

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MATERIALS AND METHODS

Collection sites

Deer blood samples were collected in the fall and winter of 1988–1989 at three sites near the metropolitan Minneapolis–St. Paul area in southwestern Minnesota, USA (Elm Creek Park Reserve, 45°10′N, 93°26′W; Minnesota Valley National Wildlife Refuge, 44°50′N, 93°14′W; and the Carlos Avery Wildlife Management Area, 45°19′N, 93°5′W; Fig. 1). Elm Creek Park Reserve is in a rural area characterized by oak-maple-basswood forest, interspersed with grasslands and wetlands. Minnesota Valley National Wildlife Refuge, surrounded by suburban and industrial development bordering the Minneapolis–St. Paul International Airport, is characterized by bottomland forests and wetlands along the Minnesota River. Carlos Avery Wildlife Management Area is in a rural area that has vegetation characteristics similar to Elm Creek. Blood samples were collected by: (1) hunters as they eviscerated their deer, (2) local game wardens or (3) the senior author from deer brought into "check stations." Age and sex were recorded by trained staff only at the Elm Creek and Minnesota Valley sites. Blood samples were allowed to clot while refrigerated (4 C) for <24 hr, centrifuged and separated by aspiration. Sera were numerically coded and shipped on dry ice to the University of Notre Dame (Notre Dame, Indiana 46556, USA) where all serologic testing was performed.

Viruses

Viruses used in serologic tests included (1) the prototype strain of CV virus (6V633) obtained from the Centers for Disease Control, Ft. Collins, Colorado, and three California serogroup isolates from Indiana: (2) JC virus strain 800245 in the 3rd suckling mouse brain (SMB) passage (Boromisa and Grimstad, 1986), (3) LAC virus strain GW-1978 in the 3rd SMB passage (Pinger et al., 1983) and (4) TVT virus strain CMWA-1978 in the 2nd SMB passage (Pinger et al., 1983).

Serologic procedures

All sera were heat-inactivated at 56 C for 30 min, and screened at a 1:2 dilution by the serum dilution neutralization (SDN) test in microtiter using Vero cells and 96-well microtiter plates. Second aliquots of positive screened sera were diluted 1:4 in medium-199 (containing Earle's balanced salt solution, gentamicin and fungizone antibiotics, supplemented with 10% fetal bovine serum), added to the test wells, and finally diluted out to 1:256 in the plates. A 100 $TCID_{50}$/0.025 ml test dose of virus was used with a 1 hr serum-virus incubation at 37 C; each serum sample was assayed the same day individually with each of the four test viruses and the end-point titer determined (fixation of cells in 10% formalin with crystal violet) following a 5-day incubation at 37 C in a 5% CO_2 atmosphere. End-point titers were expressed as the reciprocal of the highest dilution of serum which neutralized 75 to 100% of the test dose as compared with negative control serum samples. We also used heterologous test dose viruses and hyperimmune ascitic fluids as controls for cross-neutralization since cross-reactivity among the three California serogroup viruses was expected based on earlier work with a variety of vertebrate sera (Lindsey et al., 1976; Godsey et al., 1988; Grimstad et al., 1987).

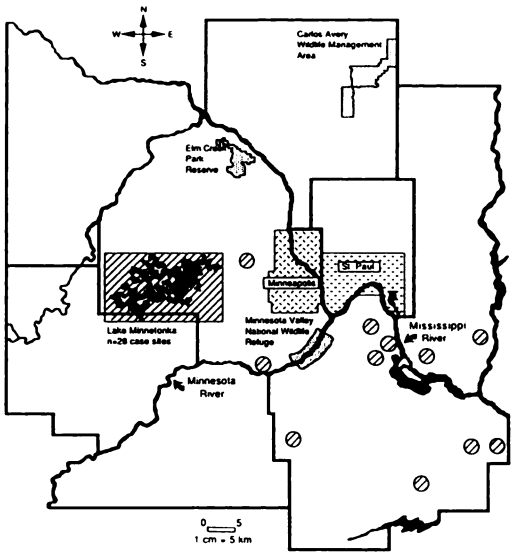

FIGURE 1. Location of three sites near metropolitan Minneapolis–St. Paul, Minnesota (USA) where deer blood collections were made and sera tested for neutralizing antibody to Cache Valley and three California serogroup viruses. Legend: ☐ Jamestown Canyon virus sampling areas; ▨ La Crosse case locations (1970–1988; n = 39 case sites); ⊡ boundary of the City of Minneapolis; ⊡ boundary of the City of St. Paul.

Serologic classification

We used the following criteria for considering a single serum sample to have specific neutralizing antibody to a California serogroup member (e.g., JC virus): (1) sera that neutralized a test dose of JC virus at a dilution of 1:4 in the SDN test and showed no cross-reactivity to either heterologous (LAC, TVT) California serogroup virus were considered seropositive; (2) sera with a SDN titer >4 to JC virus that showed a duplicative ≥2-fold higher titer to JC than to

TABLE 1. Prevalence of neutralizing antibody to Cache Valley and California serogroup viruses in fawn versus yearling and adult (older) white-tailed deer at three Minnesota sites, 1988–1989.

Site	Age group	Sample size	Cache Valley virus only	Both Cache Valley and California serogroup viruses	California serogroup only	Number sero-negative for all viruses investigated
Elm Creek	Older	55	5 (9)*	47 (85)	0 (0)	3 (5)
	Fawn	25	9 (36)	2 (8)	4 (16)	10 (40)
Carlos Avery	NA	7	1 (14)	4 (57)	0 (0)	2 (29)
Minnesota Valley	Older	30	0 (0)	25 (83)	4 (13)	1 (3)
	Fawn	21	6 (28)	1 (5)	1 (5)	13 (62)

* Number (%) positive in this age group.

either the cross-reacting LAC or TVT viruses were considered to have specific neutralizing antibody to JC virus; or (3) sera that neutralized two (or all three) California serogroup viruses at equivalent titers (using equivalent test doses) were considered to be the result of multiple California serogroup virus infection (e.g., JC and LAC, JC and TVT, or TVT and LAC). We have referred to these later sera as "California group" seropositives (Table 1). These criteria were based on long-term monitoring of the serologic conversions and anamnestic responses of captive and free-ranging deer populations (Boromisa and Grimstad, 1987; Grimstad et al., 1987; P. R. Grimstad, unpubl. data).

Age grouping of deer

For this study we separated all deer into two age groups: fawns and older deer. Fawns were those deer approximately 0.5-yr-old, while yearlings (1.5-yr-old) and adults (>1.5-yr-old) constitute the "older deer." However, separation of yearling and adult cohorts is important when multi-year sampling is done, because it allows one to calculate seroconversion rates in each year's fawn cohort (i.e., between the first and second Autumn of life).

Statistical procedures

All percentages have been rounded to the nearest whole number. *P* values were calculated using the SYSTAT subroutine TABLES (Wilkinson, 1988) for the Chi-square contingency table analysis with Yates correction. Where fitted cells were <5, we used Fisher's exact test (FET). The frequency distribution of sera having specific neutralizing antibody titers was determined for fawns and older deer at each site and for each of the four viruses we used. Where sample size was sufficient, we fit the observed frequency values to the expected using the Poisson distribution as described by Sokal and Rolf (1969) and as applied by Grimstad et al. (1984) to a human serologic survey. Long-term serologic surveys of deer harvested from populations in Indiana's JC, LAC and TVT virus enzootic regions has demonstrated that the frequency distribution of neutralizing antibody titers to these three California serogroup viruses in deer sera (and also in human sera) are best described by the Poisson distribution and that enzootic occurrence of virus infection can thus be additionally documented (Grimstad et al., 1984; P. R. Grimstad, unpubl. data). This is based on the assertion that in any animal population where a pathogen is enzootic, or endemic, and stimulates an immune response in infected hosts, "one would expect to see some high titered samples that are indicative of very recent infections, some low titered samples that are indicative of much older infections, with the majority of samples falling in between. If infections are endemic [enzootic] in the human [animal] population, they should be neutrally dispersed through time and the frequency distribution of individuals with [high] positive titers [evidence of recent infection] should be Poisson" (Grimstad et al., 1984).

RESULTS

Neutralizing antibody to both CV and one or more California serogroup virus was detected among 109 of 138 (79%) sera collected at the three sites (Table 1). Some sera were uniquely positive for a single virus. Other sera had antibody to more than one virus. No significant differences were found in the prevalence of antibody to any one virus in the yearling versus adult cohort at any site ($P > 0.05$ for all pairwise comparisons). Thus, we pooled yearling and adult data under the "older" heading (Tables 1, 2). Neutralizing antibody to both

TABLE 2. Prevalence of neutralizing antibody to Jamestown Canyon, La Crosse and trivittatus viruses in California serogroup positive fawn versus older deer at three Minnesota sites, 1988–1989.

Site	Age group	Sample size[a]	Jamestown Canyon virus	La Crosse virus	Trivittatus virus	"California group"[b]
Elm Creek	Older	47	33 (70)[c]	1 (2)	4 (9)	9 (19)[d]
	Fawn	6	3 (50)	1 (17)	2 (33)	0 (0)
Carlos Avery	NA	4	0 (0)	2 (50)	0 (0)	2 (50)[e]
Minnesota Valley	Older	29	19 (66)	1 (3)	0 (0)	9 (31)[f]
	Fawn	2	1 (50)	0 (0)	1 (50)	0 (0)

[a] See Table 1 for the total sample size of the population sampled. Sample sizes in this table are for those deer with specific antibody to one or more California serogroup viruses.

[b] The "California group" are those sera where there was <2-fold difference in titer between two or all three viruses tested (suggesting the possibility of multiple exposure to members of the California serogroup).

[c] No. (%) positive in this age group.

[d] At Elm Creek, six sera had equivalent titers for JC and TVT viruses (i.e., titers of 16 and 16, respectively), one for LAC and TVT, one for JC and LAC, and one for all three viruses.

[e] At Carlos Avery, two sera had equivalent titers for JC and LAC viruses.

[f] At Minnesota Valley, eight sera had equivalent titers for JC and LAC and one had equivalent titers for JC and TVT viruses.

CV and one or more California serogroup viruses was found in 85% (47 of 55) of the older deer at Elm Creek and 83% (25 of 30) of these animals at Minnesota Valley (Table 1). In contrast, only a few of the fawns showed specific antibody to both a California serogroup and CV virus at the two sites (8%, two of 25; 5%, one of 21, respectively) (FET for adult versus fawn: $P < 0.001$). Also, fewer fawns (17%, eight of 46) than adults (89%, 76 of 85) had California serogroup antibodies (for fawns versus adults: $\chi^2 = 64.201$, $P < 0.001$).

The prevalence of antibody to CV virus in the combined fawn cohort from Elm Creek and Minnesota Valley (39%, 18 of 46) was less than half that in the combined adult cohort (91%, 77 of 85; $\chi^2 = 37.117$, $P < 0.001$). Antibody to CV virus was more prevalent in fawn sera from both sites (39%, 18 of 46) than was antibody to all California serogroup viruses (17%, eight of 46; $\chi^2 = 4.343$, $P = 0.037$). In contrast, prevalences of antibody to both CV and California serogroup viruses were almost equal in the older deer at both sites (91%, 77 of 85 for CV virus versus 89%, 76 of 85 for California serogroup viruses; Table 1).

Specific antibody to JC virus was the most frequently detected of the California serogroup viruses for which we investigated at Elm Creek and Minnesota Valley, however, antibody to LAC virus was more frequently detected at Carlos Avery (Table 2). Of the adult deer with antibody to California serogroup viruses, 70% (33 of 47) at Elm Creek were specifically seropositive only for JC virus as were 66% (19 of 29) of the adults at Minnesota Valley (Table 2). Specific antibody only to JC virus in the total fawn cohort was less prevalent (9%, four of 46) compared to the 61% (52 of 85) in the total adult cohort sampled at these two main sites (FET for fawns versus adults: $P < 0.001$) (Tables 1, 2). Of the eight fawns at both sites with antibody to California serogroup viruses, only 50% (four of eight) were specifically seropositive for JC virus versus 91% (69 of 76) of adults (FET for fawns versus adults: $P = 0.009$); 12% (one of eight) of fawns were specifically seropositive only for LAC versus 3% (two of 76) of adults (FET for fawns versus adults: $P = 0.262$); and 38% (three of eight) of fawns were specifically seropositive only for TVT virus versus 5% (four of 76) of the adults (FET for fawns versus adults: $P = 0.017$). Twenty additional sera had equivalent titers for two or more California group viruses. These are listed as "California group" seropositives in Table 2.

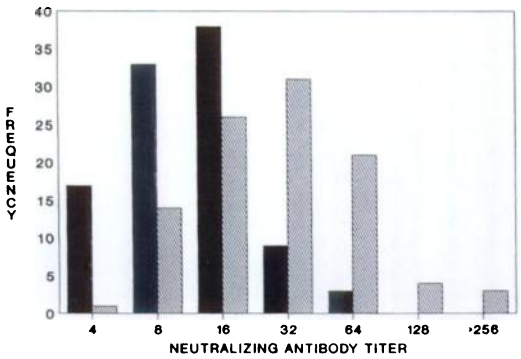

FIGURE 2. Frequency distribution of neutralizing antibody to Jamestown Canyon and Cache Valley viruses in adult Minnesota deer, 1988–1989. The frequency represents the number with specific antibody at the indicated titer of the total number seropositive for each of the two viruses. Legend: antibody to Jamestown Canyon virus ■; antibody to Cache Valley virus ▨.

Geometric mean titers (GMT) to JC virus in adults (both sites combined) were 1:11 ($n = 76$) compared with 1:28 ($n = 77$) to CV virus. Titers for JC ranged from 1:4 to 1:64, with only two titering 1:64. For CV virus, titers ranged from 1:4 to 1:256, with 21 titering ≥1:64 (Fig. 2). Titers to JC virus among the four fawns ranged from 1:4 to 1:16 (only one with a titer of 1:16) while titers to CV virus among fawns ranged from 1:4 to 1:256 (11 of 18 with titers ≥1:16).

A fit of the observed frequencies of antibody titers of adult deer to JC and to CV viruses to the Poisson distribution showed no significant difference from the expected Poisson frequencies (i.e., the number of sera with specific titers, either 1:4, 1:8 . . . , or ≥1:256) ($\chi^2 = 8.649$ with 5 df for JC virus and $\chi^2 = 9.911$ with 5 df for CV virus).

DISCUSSION

These data represent the first evidence of natural exposure of Minnesota white-tailed deer from any single population collectively to LAC, TVT, JC and CV viruses. It firmly establishes the latter two viruses as broadly enzootic in the Elm Creek and Minnesota Valley areas. Serologic evidence suggesting multiple virus infection (e.g., JC and CV, JC and TVT and CV, or JC and LAC and CV viruses) in adult deer was overwhelming while evidence of multiple infection in fawns was minimal (Table 1). In the latter case, half of the fawns seropositive for California serogroup viruses had antibody suggestive of a LAC or TVT virus infection and half had antibody to JC virus (Table 2). Low titered JC neutralizing antibody in fawns during Autumn would most likely represent residual maternal antibody derived from colostrum (Issel, 1974; Grimstad et al., 1987).

There was broad cross-reactivity among the California serogroup virus tests. We expected this based on extensive multi-year immune profile studies conducted with free-ranging and captive white-tailed deer (sera drawn from a penned herd in a JC virus focus devoid of any detectable TVT, LAC or Snowshoe Hare virus circulation) and domestic animals (Boromisa and Grimstad, 1987; Godsey et al., 1988; Grimstad et al., 1987; P. R. Grimstad, unpubl. data). However, it was possible to identify the primary California group virus infecting the majority of deer except in cases where there was less than a two-fold duplicative difference in titer (sera referred to as "California group" on Table 2).

In the multi-year monitoring of serologic conversion and anamnestic responses in Michigan penned deer, in an area where LAC and TVT viruses have not been detected, >98% of antibody titers following seroconversion of yearling deer and following anamnestic responses in reinfected adult deer, have a pattern of JC > TVT ≥ LAC (Grimstad et al., 1987; P. R. Grimstad, unpubl. data). In northern Indiana where free-ranging deer from two sites have been monitored continuously since 1982, the same general pattern exists (Boromisa and Grimstad, 1987; P. R. Grimstad, unpubl. data). In the captive herd, only six of 680 sera (from 105 individual deer) tested to date have had equivalent JC and LAC (0.6%, four of 680), or JC and TVT titers (0.3%, two of 680) or equal titers to all three viruses (0.1%, one of 680).

These LAC or TVT titers were determined to be cross-reactive based on prior and subsequent samplings from the individual animals (Grimstad et al., 1987, P. R. Grimstad, unpubl. data). This suggests that in the absence of either LAC or TVT, exceedingly few deer sera might have antibody with equivalent JC and TVT or JC and LAC titers. Only with enzootic transmission of TVT or LAC in the same area should >1% of deer have specific and equivalent titered antibody. At Minnesota Valley LAC virus circulates at low levels; one deer (3%) had specific antibody to LAC virus and eight others (27%) had equivalent JC and LAC titers. Only one deer (3%) had specific antibody to TVT virus. In contrast, at Elm Creek TVT virus circulates at higher levels; four deer (9%) were found with antibody specific to TVT and six others (11%) had equivalent antibody titers to JC and TVT viruses. However, only one deer (2%) had antibody specific to LAC virus. All four deer seropositive for the California serogroup at Carlos Avery had antibody to LAC and only two to JC virus. While the sample size is very small and no specific conclusions can be drawn from that group the results suggest that considerable transmission of LAC virus occurs there. Carlos Avery is the most rural of the sites and no human cases of LAC virus encephalitis have yet been associated with that area.

Our measurement of equivalent JC and LAC or JC and TVT titers in 25% (21 of 85) of these Minnesota deer, versus <1% occurrence in the penned herd, suggests that all three California serogroup viruses circulate in those two populations along with CV virus. However, the relatively low prevalence of antibody to LAC and TVT indicates that exposure of deer to these two viruses is much less common in the general deer population than is exposure to either JC or CV viruses. Indeed, the relatively low frequency of antibody specific to TVT virus (Table 2) also reflects the spotty annual occurrence of the primary vector, *Aedes trivittatus* (Grimstad, 1988), in the counties ringing the Minneapolis–St. Paul metropolitan area (D. F. Neitzel, unpubl. data).

Similarly, the frequency of occurrence of antibody specific to LAC virus, and sera with antibodies suggestive of past multiple (JC and LAC or LAC and TVT) virus infections in the Elm Creek (6%; five of 80 adults and fawns) and Minnesota Valley (18%; nine of 51 adults and fawns) populations (Tables 1, 2), while not significant (Elm Creek versus Minnesota Valley deer: $\chi^2 = 3.128$, $P = 0.077$), reflects enzootic transmission proximate to each site. It is important to note that the majority of pediatric LAC virus encephalitis cases in the greater Minneapolis–St. Paul region have been reported south and west of the Elm Creek site (Fig. 1; D. F. Neitzel, unpubl. data); the closest residences of confirmed LAC cases to Elm Creek are 15 km away but only 2 km from the Minnesota Valley site. This parallels the relative prevalence of antibody to JC, LAC and TVT viruses in Indiana deer as noted above where more frequent JC and LAC seropositive deer or JC and TVT seropositive deer were found in areas where either LAC or TVT was also enzootic.

Long-term monitoring of serologic conversions and anamnestic responses in multiple populations (penned and free-ranging) has shown that there is no significant difference in antibody prevalence to JC virus between yearling and adult deer from each population, and the same was true in the present study. However, antibody prevalence in fawns has always been significantly lower than that of the older deer (Boromisa and Grimstad, 1987; Grimstad et al., 1987; P. R. Grimstad, unpubl. data).

The elevated GMT and maximum titers of antibody to CV virus in older deer compared to values for JC virus probably reflect differences in seasonal transmission of each agent in Minnesota. In the upper Midwest, JC virus is transmitted to deer primarily in the mid- to late spring, coincident with the emergence of the first broods of snowmelt *Aedes* mosquitoes (Grimstad, 1988; Heard et al., 1990). This enzootic transmission often preceeds the

majority of the fawn births. Fawns are initially protected from a primary JC virus infection by maternal antibody in the colostrum for a mean of 19 wk (Issel, 1974; Grimstad et al., 1987). In contrast, free-ranging fawn and adult deer harvested in fall and early winter have relatively low antibody titers to JC (or may have become serologically negative for JC) due to decay of passively and actively acquired immunity and the distance in time from late spring mosquito transmission of JC virus (Boromisa and Grimstad, 1987; Grimstad et al., 1987; Heard et al., 1990). Older penned deer have relatively low neutralizing antibody titers to JC virus by Autumn compared to titers measured shortly after yearlings seroconvert (primary infection) or in adult deer that showed anamnestic responses on reinfection the previous spring (Grimstad et al., 1987; P. R. Grimstad, unpubl. data). In contrast, when antibody prevalence to JC virus in adult does is high, the majority of fawns killed in the same hunts are seronegative (or have minimally detectable antibody levels) because the colostrum-derived maternal antibody prevents a primary infection of fawns their first summer of life (Issel, 1974; Boromisa and Grimstad, 1987; Grimstad et al., 1987).

Cache Valley virus is transmitted later in the season to deer than is JC but more coincident with LAC and TVT viruses. Temperate North American isolates of CV virus have come primarily from mosquitoes collected between late July–October (Buescher et al., 1970; Burton et al., 1973; Heard et al., 1990; Kokernot et al., 1969). Late summer transmission of CV virus and less decay of any maternal antibody to that virus in most fawns by hunting season would result in harvested deer of all ages having relatively higher mean antibody titers to CV than to JC virus. Indeed, the maximum antibody titer to JC virus was 1:64, and in only two adult deer, compared to a titer of $\geq$1:64 to CV virus in 21 adult and three fawn deer. This suggests that CV virus infections in these Minnesota deer occurred closer to the time of harvest than did JC virus infections. Furthermore, the frequency distribution of antibody titers for JC or CV virus (Fig. 2) (best described by the Poisson distribution) parallel the pattern of human LAC virus exposure in Indiana where LAC virus is endemic (and the frequency distribution of sera with specific LAC virus antibody titers was also best described by the Poisson distribution; Grimstad et al., 1984). The high prevalence of neutralizing antibody to CV and JC viruses in Minnesota deer and the fit of the titer frequencies to the Poisson distribution suggest that both CV and JC viruses circulate enzootically. We believe that our serologic data support the hypothesis of enzootic late summer-early fall transmission of CV virus to deer versus enzootic springtime transmission of JC virus in Minnesota.

Finally, the unexpected prevalence of antibody to LAC virus in deer sera collected at Carlos Avery (Table 2) suggests that even limited sampling of sera during the Autumn may reveal new LAC enzootic foci. This information would be relevant should residential development begin there.

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