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## Jamestown Canyon Virus Seroprevalence in Endemic Regions and Implications for Diagnostic Testing

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### Abstract

**Background.** Jamestown Canyon virus, a mosquito-borne virus, can cause asymptomatic infection, febrile illness, or neuroinvasive disease in humans. Previous studies have found Jamestown Canyon virus-specific antibodies in a 4%–54% of people in various U.S. regions. To understand baseline seroprevalence in regions with the highest number of reported disease cases, we performed a serosurvey among blood donors.

**Methods.** We randomly selected blood donation specimens collected during December 2019–April 2020 from residents of counties reporting  $\geq 2$  disease cases in 2019 or 1 case in 2019

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and  $\geq 1$  case during 2010–2018. Specimens were screened for Jamestown Canyon virus–specific neutralizing antibodies and, if positive, tested for immunoglobulin M (IgM) antibodies. We estimated county population seroprevalence by calibrating sample weights to population census data.

**Results.** Fourteen counties in 3 states, Massachusetts, Minnesota, and Wisconsin, met the inclusion criteria. Within each state, average county seroprevalence ranged from 16.8% (95% confidence interval [CI], 9.3–27.0) to 18.8% (95% CI, 14.0–24.4) for Jamestown Canyon virus–neutralizing antibodies and from 7.6% (95% CI, 4.2–12.5) to 13.5% (95% CI, 9.6–18.3) for both neutralizing and IgM antibodies.

**Conclusions.** Estimated Jamestown Canyon virus seroprevalence, including for IgM antibodies, is elevated in endemic areas, complicating the interpretation of serologic testing in diagnosing acute disease in symptomatic individuals. Diagnosing Jamestown Canyon virus disease requires a high degree of clinical suspicion, ruling out other possible causes of illness, and if possible, collecting acute and convalescent samples. New assays to detect acute infection could improve diagnosis and public health surveillance for Jamestown Canyon virus disease.

### Keywords

Jamestown Canyon virus; seroprevalence; blood donor; serosurvey; diagnostic testing

## BACKGROUND

Jamestown Canyon virus is a single-stranded, negative-sense RNA virus in the California serogroup of the genus *Orthobunyavirus*. It is transmitted to humans through the bite of an infected mosquito [1]. First isolated from a pool of *Culiseta inornata* mosquitoes collected in Jamestown Canyon near Boulder, Colorado, in 1961 [2], the virus has since been isolated from a wide range of mosquito species throughout the United States [3].

Most infections are asymptomatic, but in symptomatic patients, clinical disease manifestations range from a mild febrile illness to neuroinvasive disease. Although the first human case of laboratory-confirmed Jamestown Canyon virus disease was identified in 1980 [4], it was not a reportable disease condition until 1995 when the general category of California serogroup encephalitis became nationally notifiable. Beginning in 2011, Jamestown Canyon virus disease could be reported as a distinct condition to the Centers for Disease Control and Prevention (CDC)’s ArboNET, the national arboviral disease surveillance system, using established clinical and laboratory criteria for neuroinvasive and nonneuroinvasive disease [5]. From 2011 to 2022, 282 cases of Jamestown Canyon virus disease, including 187 (66%) neuroinvasive disease cases, were reported to CDC [6]. The majority (205, 73%) of disease cases were reported from Minnesota and Wisconsin.

Seroprevalence studies in various U.S. regions have identified Jamestown Canyon virus–specific neutralizing antibodies among 4%–54% of asymptomatic persons [7–14]. Neutralizing antibodies generally confer long-lasting immunity and indicate previous infection. Although the presence of immunoglobulin M (IgM) antibodies typically indicates a recent infection, limited data demonstrate that IgM antibodies can persist for more than a

year following infection with California serogroup viruses [15]. The common presence of Jamestown Canyon virus antibodies found in previous studies combined with possible IgM persistence can lead to challenges with interpreting diagnostic test results [16]. Therefore, understanding baseline prevalence of neutralizing and IgM antibodies in asymptomatic persons can inform testing guidance and interpretation of serologic results in patients with a clinically compatible illness.

## METHODS

For this study, we defined endemic counties for Jamestown Canyon virus as those with  $\geq 2$  human disease cases reported in 2019 or 1 case reported in 2019 and  $\geq 1$  case reported during 2010–2018. We used residual serum and plasma from samples collected during December 2019 through April 2020 by the American Red Cross from unique blood donors who were residents of endemic counties. Routine informed consent was obtained at the time of blood donation and included potential use of samples and demographic information for research purposes. The protocol for this study was approved by the American Red Cross institutional review board (protocol #2021–038).

Sample size was calculated using proportional-to-size stratified sampling by county. Based on previously published seroprevalence estimates for Jamestown Canyon virus [8, 9, 11], a conservative expected seroprevalence estimate of 8% with an acceptable margin of error of 5% was specified. Samples were randomly selected from the pool of available samples to meet the number needed in each county.

Specimens were screened for the presence of neutralizing antibodies against Jamestown Canyon virus according to routine CDC diagnostic procedures using a 90% plaque reduction neutralization test at 1:10 dilution [17]. Positive specimens were serially 2-fold diluted in duplicate to determine the effective concentration for 90% neutralization ( $EC_{90}$ ) [18]. Specimens with an  $EC_{90} \geq 10$  were tested in a similar manner for neutralizing antibodies against La Crosse virus, another common arbovirus in the California serogroup. If neutralizing antibodies for both viruses were detected, infection status was classified based on viral antibody titer, with a  $\geq 4$ -fold higher titer against 1 virus than the other used to determine the more likely infection [17]. All specimens with neutralizing antibodies against Jamestown Canyon virus were also tested for Jamestown Canyon virus-specific IgM antibodies using IgM antibody capture enzyme-linked immunosorbent assay, as previously described [19].

Seroprevalence estimates and 95% confidence intervals (CI) [20] at the population level for each county with a blood donor sample size  $> 5$  were calculated by applying sample weights calibrated to the population age group distributions obtained from the 2020 U.S. Census Bureau data [21]. Because no significant differences were noted in sex distributions between blood donors and the general population, sex was not used for weighting. Age was grouped into 4 categories based on previously described methods [22]; because blood donors must be at least 16 years of age to donate, estimates were computed for the available census data population categories of  $\geq 15$  years of age. Two counties, St. Louis, Minnesota, and Marathon, Wisconsin, had no samples from donors in the youngest age group, so

county-level estimates could only be inferred for the population  $\geq 30$  years of age. Average seroprevalence estimates (95% CI) were calculated for the included areas of each state. Data were analyzed in R statistical software version 4.3.1 using the survey package v4.2 [23].

## RESULTS

Fourteen counties in three states met our criteria for Jamestown Canyon virus endemicity (Figure 1). A total of 355 specimens from three counties in Massachusetts, 7 counties in Minnesota, and 4 counties in Wisconsin were tested. Two specimens had indistinguishable neutralizing antibody titers between Jamestown Canyon and La Crosse viruses, and 64 specimens were considered specific for Jamestown Canyon virus infection with a median  $EC_{90}$  value of 80.0 (range, 10.6–1068). Of the 64 specimens, 38 (59.4%) also tested positive for Jamestown Canyon virus-specific IgM antibodies. There was no trend in the proportion of donors testing positive for Jamestown Canyon virus-specific IgM antibodies over the 5 months that specimens were collected. The proportion with Jamestown Canyon virus neutralizing antibodies increased with older age (Figure 2).

Average seroprevalence for Jamestown Canyon virus neutralizing antibodies for all sampled counties in Massachusetts ( $n = 3$ ) was 16.8% (95% CI, 9.3–27.0), for Minnesota ( $n = 7$ ) was 18.8% (95% CI, 14.0–24.4), and for Wisconsin ( $n = 4$ ) was 18.0% (95% CI, 10.9–27.1). At a county level, seroprevalence estimates were similar in endemic counties with more than 10 samples tested (Figure 3). The highest seroprevalence estimates were seen in the 2 counties in which samples were not available from young blood donors, namely St. Louis County in Minnesota (91%; 95% CI, 70.9–99.0) and Marathon County in Wisconsin (47.2%; 95% CI, 15.7–80.5).

Average seroprevalence for Jamestown Canyon neutralizing and IgM antibodies for all sampled counties in Massachusetts was 9.3% (95% CI, 3.8–18.3), for Minnesota was 13.5% (95% CI, 9.6–18.3), and for Wisconsin was 7.6% (95% CI, 4.2–12.5). Similar trends were observed in seroprevalence of IgM antibodies as the neutralizing antibodies in counties with more than 10 samples tested (Figure 4). However, the proportion of specimens testing positive for IgM antibodies of those with neutralizing antibodies varied and ranged from 33% in Essex, Massachusetts, to 100% in St. Louis County, Minnesota.

## DISCUSSION

We found that roughly 1 in 5 blood donors living in Jamestown Canyon virus endemic areas in this study had evidence of prior infection, and about half of those with evidence of prior infection also had IgM antibodies. Our county population estimates in different states were relatively consistent, averaging approximately 18% overall for neutralizing antibodies and 10% for neutralizing and IgM antibodies. However, there was some variability in the seroprevalence estimates by county that is likely linked to the type and density of vectors and hosts circulating the virus in an area [10, 24]. The relatively high baseline seroprevalence, particularly for Jamestown Canyon virus IgM antibodies in endemic areas, highlights the need to assess the pretest probability of Jamestown Canyon virus disease in a patient when considering testing and interpreting results.

Almost all of our seroprevalence estimates were within the range of those reported in populations in various U.S. regions of 4% to 54% [7–14]. For example, a study of U.S. National Park and Forest Service employees during 2008–2010 found an overall Jamestown Canyon virus neutralizing antibody seroprevalence of 14.6%, ranging from 6.7% in southeast regions to 21.7% in western regions [10]. We found higher seroprevalence estimates in areas where older blood donors were sampled and that the proportion of blood donors having antibodies increased with increasing age, suggesting the virus has been present in these areas for decades, if not longer.

The common presence of Jamestown Canyon virus IgM antibodies among asymptomatic persons with evidence of previous infection indicates these antibodies might persist well beyond acute infection. IgM antibody persistence has been documented with several viruses in the flavivirus genus, such as West Nile and Zika viruses [25, 26]. However, our seroprevalence estimates for Jamestown Canyon virus are considerably higher than those for other arboviruses [27–30]. Most blood donor samples in this study were collected from northern states during January–March, demonstrating that Jamestown Canyon virus infections were likely acquired during the previous season 4 to 8 months before or even an earlier mosquito season, as Jamestown Canyon virus transmission peaks in July–September [31]. In a study of 15 patients in Canada with laboratory-confirmed Jamestown Canyon or Snowshoe Hare virus infections, all had persistent IgM titers for more than a year, and several had IgM persistence for 2–5 years [15]. The study also found IgM positivity of 9% among 90 randomly selected patients during the winter months in Canada. Although molecular testing to identify viral RNA might assist in identifying acute infections, it has limited utility given the transient nature of viremia with arboviral infections in immunocompetent individuals [32–34].

Our study has several limitations. First, the blood donor sample size for several counties was relatively small, limiting the precision of the estimates and the generalizability to the county population. The blood donor age distribution also only allowed extrapolation to the adult population. Second, our estimates only included areas that had recent Jamestown Canyon virus disease cases reported to CDC and thus might not be generalizable to other areas. Finally, transmission of Jamestown Canyon virus by blood transfusion has not been identified to date, and this seroprevalence study was not designed to assess potential risk to the blood supply.

## CONCLUSIONS

Given that Jamestown Canyon virus seroprevalence in endemic areas is relatively high, detection of these antibodies might not correlate with acute illness, particularly in older patients and in certain areas [16]. Therefore, the gold standard of serologic diagnosis of recent infection should be to test acute and convalescent sera to assess for  $\geq 4$ -fold change in neutralizing antibody titer [17, 35]. Because convalescent sera are often difficult to obtain, a high pretest probability, including having a clinically compatible illness, exposure history, and lack of an alternative diagnosis, is important for the accurate diagnosis and reporting of Jamestown Canyon virus disease. Additional studies to assess IgM duration following Jamestown Canyon virus infection and new testing strategies to determine timing

of infection could improve diagnosis and public health surveillance for Jamestown Canyon virus disease.

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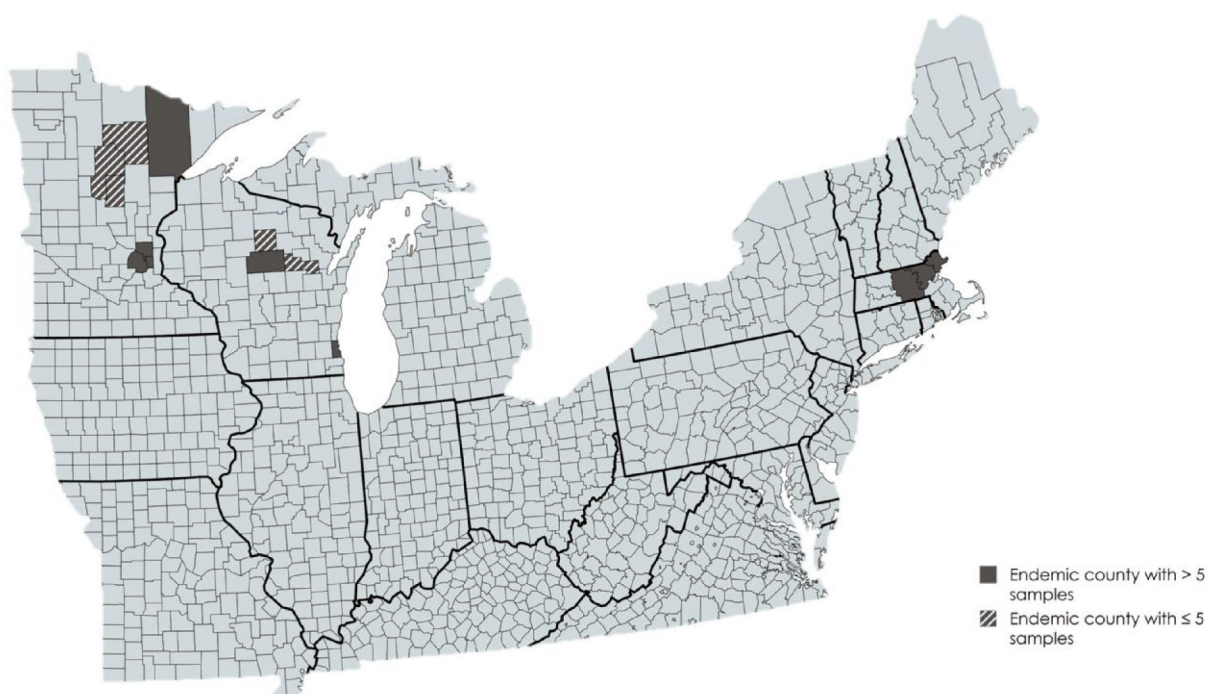


**Figure 1.**  
Counties included in the study. Source: Created with [mapchart.net](https://mapchart.net).

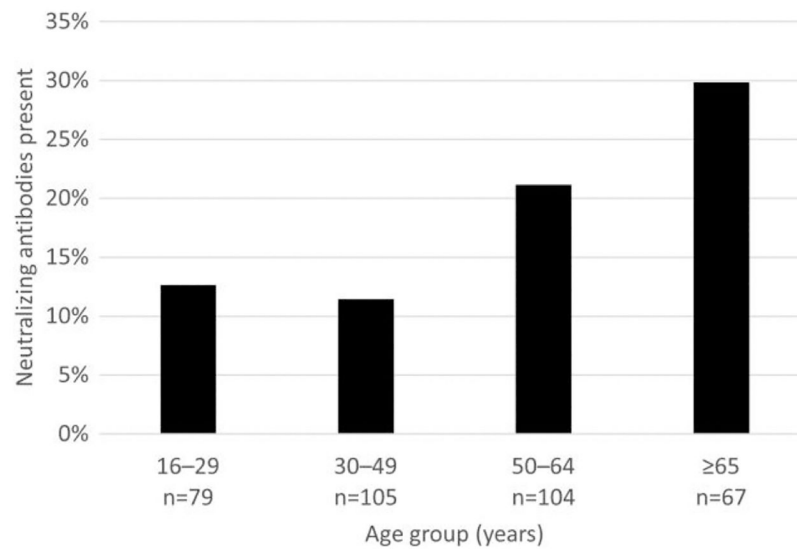
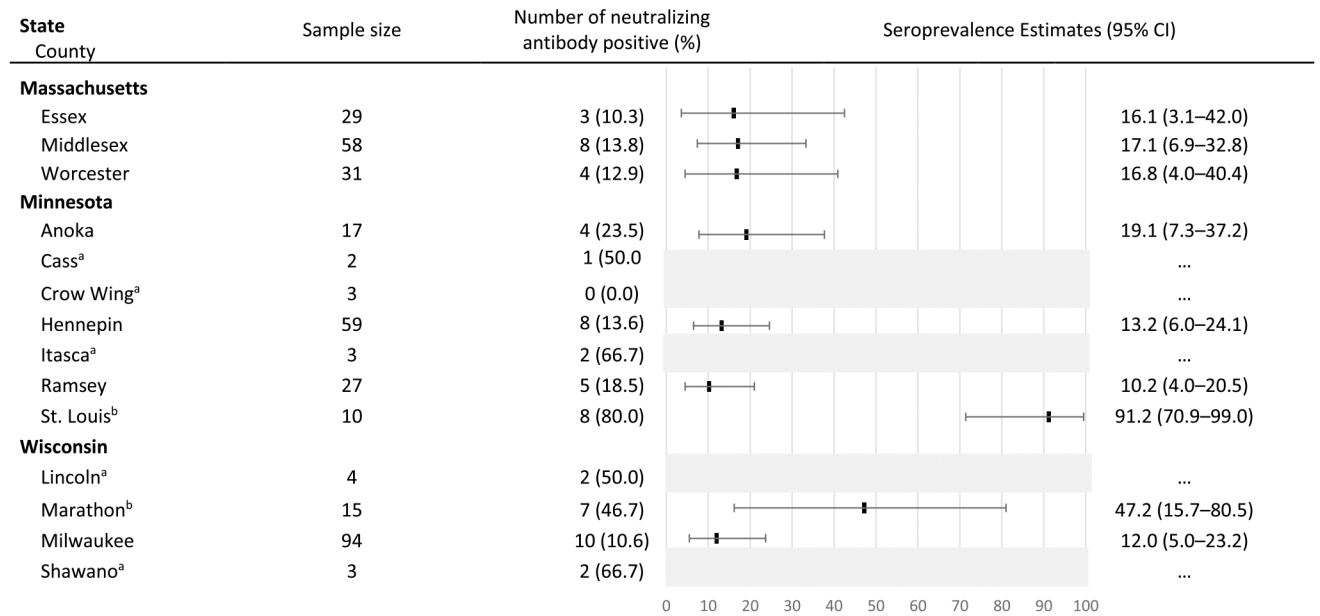


**Figure 2.**  
Percent of sampled blood donors positive for Jamestown Canyon virus neutralizing antibodies by age group.

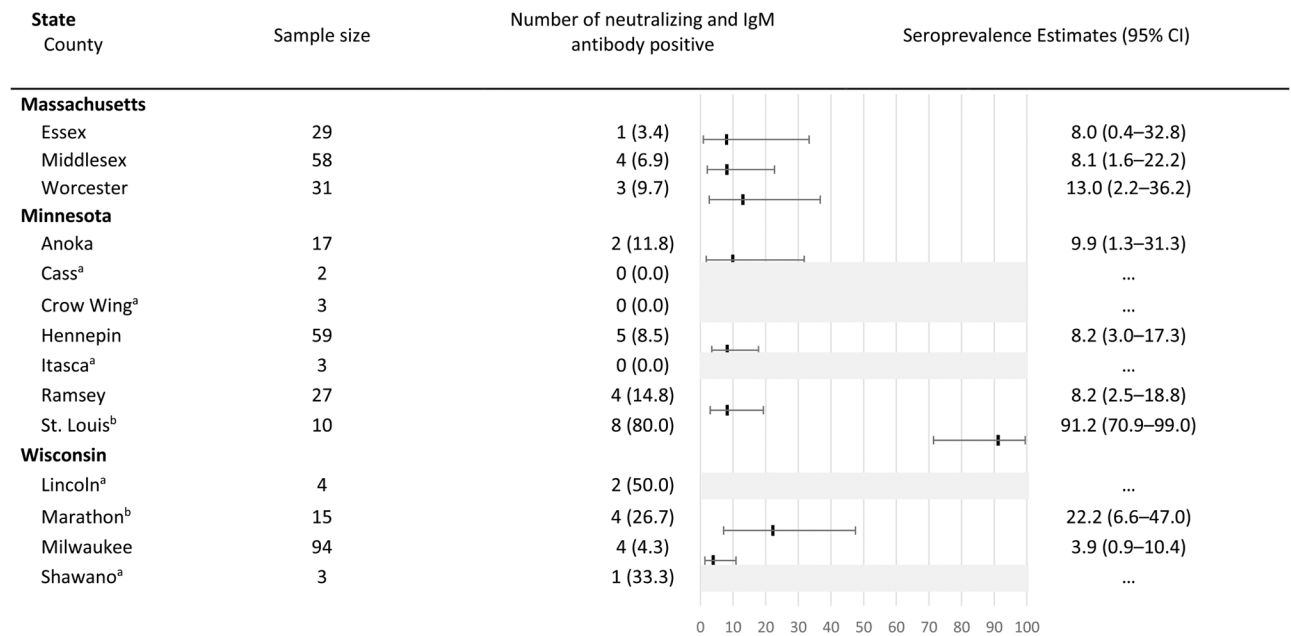


Abbreviation: CI, coincidence interval.

<sup>a</sup>County seroprevalence estimates not calculated because sample size is ≤5.

<sup>b</sup>County estimate only represents the population 30 years of age and older.

**Figure 3.**  
Jamestown Canyon Virus Neutralizing Antibody Test Results in Blood Donor Samples and  
Population Seroprevalence Estimates by State and County, December 2019–April 2020.



Abbreviation: CI, coincidence interval.

<sup>a</sup>County seroprevalence estimates not calculated because sample size is ≤5.

<sup>b</sup>County estimate only represents the population 30 years of age and older.

**Figure 4.**

Jamestown Canyon Virus Neutralizing and Immunoglobulin (Ig)M Test Results in Blood Donor Samples and Population Seroprevalence Estimates by County, December 2019–April 2020.