Comparison of Enzootic Risk Measures for Predicting West Nile Disease, Los Angeles, California, USA, 2004–2010

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West Nile virus (WNV; family Flaviviridae, genus Flavivirus) is amplified within a mosquito–bird cycle, with tangential transmission to equids and humans (1). Since the introduction of WNV into Los Angeles, California, USA, in 2003, our research (2–5) has focused on surveillance indicators for enzootic WNV transmission and prediction of human cases. The Greater Los Angeles County Vector Control District (GLACVCD) serves >6 million of the ≈10 million residents of Los Angeles County and conducts year-round surveillance for WNV activity (6). In addition to having a robust surveillance dataset, Los Angeles County is a suitable location for evaluating environmental risk because the large human population enables the sensitive detection of dead birds (7), increases opportunities for human–vector contact, and experienced 2 outbreaks during the study period (6).

We compared the predictive ability of 3 measures of human risk by using time-series graphs, sensitivity, specificity, positive predictive value (PPV), and concordance between human case onset and states of high risk based on enzootic transmission during 2004–2010. We believed that for operational decision support a successful risk measure should correctly 1) identify periods of low risk when few or no cases occur, 2) predict high or increased risk before human cases occur, and 3) identify periods of high risk concurrent with the occurrence of human cases.

The 3 measures of risk we compared were the California Mosquito-Borne Virus Risk Assessment (CMVRA), the vector index, and the Dynamic Continuous-Area Space-Time (DYCAST) system. The CMVRA (8) calculates risk on the basis of ranks of environmental variables for enzootic WNV transmission and is used by health agencies throughout California to measure risk. At its inception, the CMVRA was evaluated retrospectively for its ability to detect cases of Western equine encephalomyelitis virus (family Togaviridae, genus Alphavirus) and St. Louis encephalitis virus (family Flaviviridae, genus Flavivirus) in California during low-, medium- and high-risk seasons (9). Additional assessment of the ability of CMVRA to track WNV cases in Bakersfield, California, produced impressive results during 2004 and 2007 (10,11).

The second method was the vector index, an estimate of the number of infected mosquitoes collected per trap-night. This index successfully determined human risk in Colorado (12,13) and is used by the Colorado Department of Public Health and Environment (www.cdphe.state.co.us/dc/zoonosis/wnv/wnvsentinel.html).
The third method was the DYCAST (14) system, which provides an assessment of risk in time and space by
using reports of dead birds from the California Department of Public Health Dead Bird Hotline. This risk estimate
differs from the previous 2 in that the spatial scale is fine
(0.44 km² grid cells), it is computationally more complex,
and it does not rely on laboratory test results (15).

Understanding the characteristics of risk estimates to
determine the best predictive measure for human cases is
needed for several reasons. First, reducing the rate of false-
positive results will reduce message fatigue associated with
repeated false warnings of high-risk conditions. Second,
increasing the proportion of high-risk areas correctly
identified (sensitivity) can reduce the costs associated
with emergency mosquito control by correctly focusing
timely intervention. Third, a qualitative assessment of
risk estimates that incorporates different variables for
enzootic transmission enables understanding of the ability
differs from the previous 2 in that the spatial scale is
of different assemblages of surveillance data for predicting
human risk. Overall, a better understanding of the tools
used in decision support for emergency intervention can
only improve the protection of human health.

Materials and Methods

The epidemiology of WNV in Los Angeles has been
described in detail (6). Methods used for data collection
for each risk assessment tool are summarized briefly below
and in detail (online Technical Appendix, wwwnc.cdc.gov/
EID/pdfs/11-1558-Techapp.pdf).

CMVRA

The CMVRA (8) calculated risk on the basis of
average daily temperature, mosquito abundance and
infection, counts of WNV RNA–positive dead birds, and
sentinel chicken seroconversions over successive 2-week
periods. Each variable was assigned to quintile ranks, and
these categorical values were averaged to calculate a final
risk estimate. Thresholds ≤2.5 were considered low-risk
(normal season) conditions; those 2.6–4.0 were considered
medium-risk (emergency planning) conditions; and those
≥4.1 were considered high-risk (epidemic) conditions.

Details of sampling, laboratory testing, and risk
calculation are summarized in the online Technical
Appendix. In the current study, temperature data were
aggregated from the National Aeronautics and Space
Administration Terrestrial Observation and Prediction
System (16) at a 1-km² scale for the GLACVCD jurisdiction.
Abundance anomalies for Culex pipiens quinquefasciatus
mosquitoes collected by gravid traps (6) were calculated
by comparing current 2-week estimates to 5-year averages
for the same period. WNV infection incidence in Cx. p.
quincefasciatus mosquitoes was calculated from mosquito
pool data by using the Excel (Microsoft, Redmond, WA,
USA) add-in developed by Biggerstaff (17). Dead birds
reported by the public and testing positive for WNV
RNA and sentinel chicken seroconversions were ranked
according to frequency and scale of occurrence for the
broad region (Los Angeles County) and the specific region
(within GLACVCD jurisdiction). Reports of sentinel
chicken seroconversions from Los Angeles County outside
the GLACVCD boundary were found on the California
West Nile virus Web site (www.westnile.ca.gov). Human
cases, recorded by the Los Angeles County Department
of Public Health, Acute Communicable Disease Control,
were excluded from the current risk calculations because
they were used as an outcome measure.

Vector Index

The vector index also was calculated for 2-week time
steps by using abundance (numbers per gravid trap per
night) and infection incidence for Cx. p. quinquefasciatus
mosquitoes collected by gravid traps by using the bias-
corrected maximum-likelihood estimate (6) (online
Technical Appendix). Usually the species-specific
maximum-likelihood estimate is multiplied by female
mosquito abundance measured by CO2 trap counts to yield
an arbovirus equivalent of the entomologic inoculation rate
in malaria epidemiology (18). Vector index estimates were
stratified into frequency percentiles by using SAS version
9.1 software (SAS Institute Inc., Cary NC, USA), and the
percentiles were assessed individually for their efficacy for
predicting human cases.

DYCAST

For DYCAST, 0.44-km² grid cells were overlaid onto
the Los Angeles County study area. There were 22,687
grid cells in Los Angeles County, but only 6,666 grid cells
were within the GLACVCD boundary. We assessed the
DYCAST risk estimates by using a predetermined Knox
test significance threshold of ≈0.10 = high risk. The Knox
test statistically delineated significantly positive groups
of grid cells into clusters or hot spots. Unlike the other 2
methods, the DYCAST model assessed risk on a daily basis,
providing a time and location of high risk on the basis of
the spatial grouping of the number of reports of dead birds;
data were independent of a predetermined spatial allocation
of sampling assets and laboratory diagnostics. To make
this method comparable with the previous 2 methods, we
selected the minimum DYCAST value by grid for each
2-week period. The DYCAST model then was assessed by
using daily and 2-week aggregations.

Another unique feature of the DYCAST model is
the spatial resolution. The other 2 methods provide an
assessment of high-risk conditions that can be anywhere
within the GLACVCD boundary, whereas DYCAST
delineates high-risk conditions within a defined space.
Again, to make our assessments comparable, we aggregated DYCAST high- and low-risk cells spatially by week, up to the spatial limit imposed by the GLACVCD boundary (6,666 cells). The new spatial aggregates were compared with human case occurrence to determine an optimal number of grid cells needed to establish a high-risk area. This comparison was performed by constructing a receiver operator characteristic (ROC) curve of the plotted sensitivity versus 1 – specificity for all aggregated cell counts.

Reports of Human Cases

Reports of laboratory-confirmed human cases, compiled by the Acute Communicable Disease Control program of the Los Angeles County Department of Public Health and occurring within GLACVCD, included West Nile fever (WNF) and West Nile neuroinvasive disease (WNND) diagnoses and asymptomatic viremic blood donors. Onset dates for symptomatic persons were adjusted backward 10 days to account for the intrinsic incubation period (19,20). Seven blood donors with viremia later became symptomatic for WNV disease and were added as WNV cases; the mean time from donation to symptom onset was 6.2 days (SD ±6.14, median 3.5). To account for earlier detection, the infection dates for all viremic blood donors were adjusted backward 4 days (10 latent days minus 6 induction days). As reported for Los Angeles County (6), the percentage of WNND among all reported WNV infections increased significantly over time because of reduced physician requests for laboratory testing for febrile illness, thereby reducing the total number of human cases reported. In addition, unpublished data from elsewhere in California also indicate that relatively few persons hospitalized with neuroinvasive disease are tested for WNV, which possibly also indicate that relatively few persons hospitalized with human cases were identified; specificity was the proportion of low-risk periods correctly identified (21). The PPV, likelihood ratio positive, and likelihood ratio negative were calculated as measures of relative precision (22).

ROC curves were plotted to define optimum response thresholds. The area under the curve (AUC) was calculated to compare the 2 methods. ROC and AUC calculations were performed by using SAS version 9.1 and the Macro %ROC (http://support.sas.com/kb/25/addl/fusion25017_5_roc.sas.txt).

With the above analyses providing information about the accuracy of each risk assessment, a separate case-crossover study was performed by using the known onset information to create an estimate of the relative risk of acquiring WNV during high-risk periods. Illness onset dates for case-patients and asymptomatic viremic blood donors were lagged backward as described above. Mantel-Haenszel relative risks were calculated to determine whether high-risk values were significantly associated with human infection (23–25). Mantel-Haenszel relative risks were calculated by using the proportion of high-risk periods before estimated infection as the expected frequency of exposure and the concordance odds of disease transmission occurring during a high-risk period by each model and threshold. Data aggregation and zonal statistics were performed by using PostgreSQL 8.3.7 and PostGIS 1.3.1.

Results

CMVRA

Risk estimates (Figure 1, panel A) consistently reached emergency planning thresholds (threshold ≥2.6) before human case detection. In 2004, epidemic thresholds (≥4.1) were reached by mid-August (Table 1) after 39 human cases had been reported. During the second epidemic in 2008, risk assessments reached epidemic thresholds after 8 human cases were identified. Using the epidemic threshold, we identified 13 true-positive intervals, 0 false-positive intervals, 151 true-negative intervals, and 28 false-negative intervals. Estimates using this method were driven by ranks for environmental conditions and infections in dead birds, followed by mosquito infection rates and abundance. Antecedent sentinel chicken seroconversions consistently ranked lowest on the 5-point scale until human cases occurred because they were temporally concordant (26).

Using the emergency planning threshold, we identified 40 true-positive intervals, 28 false-positive intervals, 123 true-negative intervals, and 1 false-negative interval. Although there were more false-positive intervals, they represented high-risk periods before the onset of human cases because the threshold reached ≥2.6 at least 2 weeks before human cases occurred in all study years except 2008.
Predicting West Nile Disease (Table 1). On the basis of the advance warning that this risk estimate provided and the increase in sensitivity (Table 2), the 2.6 threshold was a better threshold for epidemic prediction.

We calculated sensitivity and specificity separately for each study year by using the 2.6 emergency planning threshold (Table 3). Use of this test validity revealed that sensitivity, i.e., correctly identified high-risk periods, dipped in 2005, whereas specificity, i.e., proportion of correctly identified low-risk periods, was lowest in 2006 and 2008.

Vector Index

Vector index estimates (Figure 1, panel B) were calculated biweekly for the entire study period for Cx. p. quinquefasciatus mosquito collections and were driven exclusively by mosquito infection incidence. Using the 65th percentile (0.018) as the threshold, we identified 38 true-positive, 37 false-positive, 116 true-negative, and 1 false-negative intervals. The frequency distribution of the vector index was highly right skewed and could not be evaluated at lower percentiles because all other percentiles were 0. The vector index increased and remained >0.095 (85th percentile) 4 weeks before the onset of human cases in 2004, 2009, and 2010 and 2 weeks before case onset in 2005 and 2006 (Figure 1, panel B). The sensitivity and specificity of the vector index, calculated annually (Table 3), demonstrated that sensitivity was lower than for the CMVRA in all study years except 2009 and 2010, with the lowest value (0.500) in 2007. The specificity of the vector index was consistently better than that of the CMVRA, except for 2009 and 2010, when only 2 human cases occurred.

DYCAST

Positive DYCAST cells were observed before human case occurrence in 5 of the 7 study years (Table 1). Counts of positive DYCAST grid cells compared with human case onset is presented in Figure 1, panel C. The DYCAST risk estimate, calculated by grouping the biweekly estimates, was used in the yearly comparisons of sensitivity and specificity (Table 3). Temporal changes in sensitivity and specificity showed the impact of reduced reporting of dead birds over time because the values for both measures of validity were highest in 2004 and declined to 0 or near 0 in all subsequent years.

Human Case Reports

A total of 389 cases of WNV disease were reported during the study period. Of these, 14 reports were missing onset date information and were not used to evaluate the risk estimates.

Analysis

The proportion of high-risk intervals correctly identified (sensitivity) was greatest in the CMVRA when the 2.6 emergency planning threshold was used (Table 2). The vector index provided the second highest sensitivity by using values just >0 (65th percentile). The greatest specificity, i.e., proportion of low-risk intervals correctly identified, was observed in the CMVRA at the epidemic threshold of 4.1, followed by the vector index at the 95th percentile.
percentile; the PPV followed this finding. The likelihood ratio positive, i.e., the likelihood that a high-risk condition was identified correctly when a human case occurred, was greatest for the vector index at the 95th percentile. The likelihood ratio negative, i.e., how much the odds of a human case decrease during low-risk conditions, was lowest in the emergency planning threshold of the CMVRA.

Discriminatory ability, as measured by the AUC, was greatest for the CMVRA (0.982), followed by the vector index (0.845) (Figure 2). Ideal response level cutoffs for the CMVRA as indicated in the ROC plots would be 1.8 and 2.6. The ideal response level for the vector index was more difficult to identify because of the obvious tradeoff between the sensitivity and specificity as evidenced in the ROC plot. The DYCAST cell aggregates performed no better than chance with an AUC of 0.468, with worst performance occurring when a single positive cell was used to assess risk.

A case-crossover study was conducted for all cases and asymptomatic blood donors with a known illness onset or donation date. The relative risk, i.e., risk for WNV infection given exposure to high-risk conditions, was greatest when detected by the CMVRA by using the emergency planning threshold (Table 2).

Discussion

Since the introduction of WNV into the United States in 1999, WNF and WNND have caused at least 31,365 illnesses and 1,250 deaths (27). Once considered to be a mild influenza-like illness, WNF is now understood to be an acute viral infection, often followed by months of illness associated with depression, altered moods,
headaches, and fatigue (28–30). The illness associated with WNND, including meningitis, encephalitis, and acute flaccid paralysis, has been associated with persistent motor and cognitive deficits and incomplete recovery (28,31). Reported cases of WNF and WNND underrepresent the actual number of WNV cases in the U.S. population (32,33), and symptomatic persons represent only a fraction of those infected. In addition to individual suffering, the medical and public health costs associated with WNV average >$40,000 per case (of those infected. In addition to individual suffering, the medical and public health costs associated with WNV average >$40,000 per case (34) at a time when many health agencies are facing serious budgetary shortfalls.

The individual health toll and associated medical costs present a strong case for active intervention. Current means to prevent WNV infection include integrated vector management by larval mosquito control to arrest viral amplification and, in an outbreak, ground or aerial adulticide applications to eliminate infectious female mosquitoes and personal protection to avoid mosquito bites. Emergency application of adulticides became particularly controversial in California (35), even though it is the only method that targets mosquitoes capable of transmitting virus and is cost-effective for preventing human cases (36). In light of this controversy, mosquito control agencies in California are often hesitant to apply adulticides until epidemics appear imminent on the basis of available risk estimates or the occurrence of human cases. Our study comparatively evaluated 3 risk measures currently used as decision support tools for intervention and for predicting human cases.

By using only indicators of enzootic transmission, the CMVRA consistently produced estimates in the emergency planning range before human case occurrence; however, epidemic thresholds were not reached until after human cases had been detected. Risk assessment by this method required a robust arboviral surveillance program, with regular sampling for multiple surveillance indicators. The specificity and PPV when the epidemic threshold of 4.1 was used were excellent; however, this was at the expense of adequate lead time for initiating intervention efforts before some human cases. Additionally, the sensitivity of the risk estimate was less than desirable at 0.317, meaning that fewer than one third of the high-risk periods were correctly identified. The CMVRA using the 4.1 threshold was poor at predicting high-risk intervals but good at predicting low-risk intervals.

The 2.6 emergency planning threshold for the CMVRA increased sensitivity and provided a predictive indication of human cases before their onset. The likelihood ratio positive was better than the DYCAST risk estimates, and the likelihood ratio negative was the best of all methods. In addition, the associated risk for human cases, measured by the Mantel-Haenszel relative risk, was the greatest. At the 2.6 emergency planning threshold, the CMVRA was excellent at predicting high-risk periods and good at predicting low-risk periods.

The vector index was simple to calculate and required only a mosquito surveillance and testing program, thereby saving costs associated with sentinel chicken maintenance and sampling and dead bird reporting and testing programs. Unfortunately, this measure did not have preestablished risk thresholds. In our study, it appeared that setting the threshold to >0 (i.e., whenever mosquito infection was detected) would be adequate for predicting human cases in urban settings, such as Los Angeles, California, USA*.

Table 2. Comparison of CMVRA, vector index, and DYCAST for predicting risk for West Nile disease by the calculation threshold applied, validation method, and associated risk, Los Angeles, California, USA, 2004–2010*

<table>
<thead>
<tr>
<th>Model</th>
<th>Sen</th>
<th>Spe</th>
<th>PPV</th>
<th>LRP</th>
<th>LRN</th>
<th>Mantel-Haenszel RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMVRA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.6</td>
<td>0.976</td>
<td>0.815</td>
<td>0.588</td>
<td>5.261</td>
<td>0.03</td>
<td>403.453 (70.506–2,308.659)</td>
</tr>
<tr>
<td>4.1</td>
<td>0.317</td>
<td>1</td>
<td>1</td>
<td>UND</td>
<td>0.683</td>
<td>38.255 (29.425–49.736)</td>
</tr>
<tr>
<td>Vector index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(percentile)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0.018 (65)</td>
<td>0.974</td>
<td>0.758</td>
<td>0.507</td>
<td>4.029</td>
<td>0.034</td>
<td>25.251 (18.120–35.033)</td>
</tr>
<tr>
<td>0.041 (75)</td>
<td>0.846</td>
<td>0.902</td>
<td>0.688</td>
<td>8.631</td>
<td>0.171</td>
<td>25.383 (18.350–35.112)</td>
</tr>
<tr>
<td>0.096 (85)</td>
<td>0.564</td>
<td>0.954</td>
<td>0.759</td>
<td>12.33</td>
<td>0.457</td>
<td>24.284 (17.503–33.692)</td>
</tr>
<tr>
<td>0.276 (95)</td>
<td>0.246</td>
<td>0.993</td>
<td>0.909</td>
<td>36.231</td>
<td>0.748</td>
<td>23.253 (16.878–32.036)</td>
</tr>
<tr>
<td>DYCAST</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>0.268</td>
<td>0.165</td>
<td>&lt;0.001</td>
<td>0.321</td>
<td>4.443</td>
<td>10.112 (7.367–13.880)</td>
</tr>
<tr>
<td>Biweekly</td>
<td>0.361</td>
<td>0.045</td>
<td>0.006</td>
<td>0.378</td>
<td>14.242</td>
<td>9.756 (7.764–12.258)</td>
</tr>
</tbody>
</table>

*CMVRA, California Mosquito-Borne Virus Risk Assessment; DYCAST, Dynamic Continuous-Area Space-Time system; Sen, sensitivity; spe, specificity.

Table 3. Comparison of the sensitivity and specificity of CMVRA calculated at the emergency planning threshold of 2.6, the vector index calculated at the 80th percentile, and DYCAST risk estimates aggregated weekly for detecting risk for West Nile disease, Los Angeles, California, USA*

<table>
<thead>
<tr>
<th>Model</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sen</td>
<td>Spe</td>
<td>Sen</td>
<td>Spe</td>
<td>Sen</td>
<td>Spe</td>
<td>Sen</td>
</tr>
<tr>
<td>CMVRA</td>
<td>1</td>
<td>0.667</td>
<td>0.857</td>
<td>0.647</td>
<td>1</td>
<td>0.556</td>
<td>1</td>
</tr>
<tr>
<td>Vector index</td>
<td>0.778</td>
<td>0.867</td>
<td>0.714</td>
<td>0.941</td>
<td>0.667</td>
<td>0.5</td>
<td>0.8</td>
</tr>
<tr>
<td>DYCAST</td>
<td>0.517</td>
<td>0.268</td>
<td>0.034</td>
<td>0.143</td>
<td>0</td>
<td>0.063</td>
<td>0</td>
</tr>
</tbody>
</table>

*CMVRA, California Mosquito-Borne Virus Risk Assessment; DYCAST, Dynamic Continuous-Area Space-Time system; Sen, sensitivity; spe, specificity.
Los Angeles, where *Cx. p. quinquefaciatus* mosquitoes are the primary vectors and temperatures generally permit viral amplification. The estimates of the vector index increased before case occurrence in 5 of the 7 years. The sensitivity and specificity were comparable with those of the CMVRA, but the likelihood ratio positive was the greatest of all risk estimates. The likelihood ratio negative was better than that of the DYCAST but not as good as that of the CMVRA. Therefore, the vector index was moderate at predicting high-risk periods and very good at predicting low-risk periods. The measure of risk associated with a high-risk value, assessed by the Mantel-Haenszel relative risk, was also better than the DYCAST risk estimate but not as good as either CMVRA threshold.

The DYCAST risk estimate was useful in years with amplified enzootic transmission, when dead birds were considered the primary WNV surveillance indicator (4,37–39). However, after the initial epidemic, WNV activity has been progressively more difficult to predict by using DYCAST because of reduced reporting to the California Dead Bird Hotline. Whether this decrease resulted from truly decreased numbers of dead birds as bird populations became progressively more resistant to infection or to public apathy/decreased awareness was not possible to ascertain. Losing time precision by aggregating estimates clearly increased measures of validity, which considering the uncertainty regarding time between WNV exposure and disease onset seemed appropriate to improve predictive power. The sensitivity of the weekly DYCAST risk estimate was similar to that of the CMVRA, but the specificity, PPV, likelihood ratio positive, and likelihood ratio negative were all uniformly worse than the other 2 methods, even when aggregated spatially. Additionally, the measure of relative risk associated with risk estimates was less than that of the CMVRA and the vector index.

In conclusion, critical decisions on intervention by using risk estimates require knowledge of the strengths and weaknesses of the selected method to respond in an adequate and timely manner to prevent human cases while reducing unnecessary response and costs associated with falsely identified high-risk periods. The goals we set for a good WNV risk estimate were a balance of these attributes and were achieved best in urban and suburban Los Angeles by the CMVRA by using the 2.6 epidemic planning threshold. In light of this finding, an evaluation of the CMVRA should be done in other ecologic settings with transmission driven by other vector species to determine whether the threshold should be adjusted to provide better antecedent estimates of human risk.

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Predicting West Nile Disease

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