Differential West Nile Fever Ascertainment in the United States: A Multilevel Analysis

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Abstract. We evaluated the completeness of West Nile fever (WNF) surveillance within the U.S. public health system. We surveyed laboratory and surveillance programs on policies, practices, and capacities for testing, confirmation, and reporting (collectively called ascertainment) from 2003 through 2005. We calculated syndrome ascertainment ratios by dividing WNF counts by neuroinvasive disease counts; separately, we performed multilevel modeling. Jurisdictions were more likely to ascertain at least one WNF cases per West Nile neuroinvasive disease case when ≤ 1 testing restrictions existed (odds ratio [OR] = 7.7, 95% confidence interval [CI] = 1.3–46.4), when conducting ≥ 4 activities to enhance reporting (OR = 9.3, 95% CI = 1.6–54.8), and when ≥ 5.0 staff per million residents were dedicated to arboviral surveillance (OR = 6.4, 95% CI = 1.0–40.3). Ascertainment of WNF was less likely among Blacks (OR = 0.56, 95% CI = 0.31–0.99) and Hispanics (OR = 0.69, 95% CI = 0.48–0.98) than among Whites. Ascertainment was more complete when testing and reporting were enhanced, but differentially incomplete for minorities.

INTRODUCTION

West Nile virus (WNV) infection is associated with a spectrum of disease severity. Most infections do not cause symptomatic illness and less than 1% result in severe West Nile neuroinvasive disease (WNND), including encephalitis, aseptic meningitis, and flaccid paralysis.¹ Approximately 20% of infections result in West Nile fever (WNF), which is a syndrome typically characterized by acute fever, headache, and fatigue. The potential duration,² severity,^{3,4} and neuropsychologic sequelae^{5,6} associated with WNF have been documented through case series.

The emergence of WNV in the United States was first detected in the New York City metropolitan area in 1999.⁷ By the end of 2003, more than 14,000 human WNV cases had been reported in 45 states.⁸ The unprecedented size of the epidemic often exceeded the U.S. public health system's laboratory testing and surveillance capacities for arboviral illness.⁹ The absence of commercially available assays to detect WNV infection in clinical settings intensified the initial demand for serologic testing within public health laboratories, and patients with WNND often were prioritized when testing volumes were high. When enzyme immunoassays tests for antibodies against WNV became commercially available in 2003, testing options increased but the specificity of some tests was not optimal.¹⁰ Serologic cross-reactivity from previous flavivirus infection¹¹ and the persistence of WNV-specific IgM in serum and cerebrospinal fluid^{12–14} necessitated case confirmation with arboviral panels, plaque-reduction neutralization tests, and convalescent-phase serum testing. In addition, incomplete disease reporting¹⁵ and physicians' lack of awareness of reporting procedures^{16–18} required added efforts to enhance surveillance.⁹

West Nile fever was designated nationally notifiable in 2004 after the Centers for Disease Control and Prevention (CDC)

endorsed a Council of State and Territorial Epidemiologists (CSTE) position statement to expand the surveillance case definition to include non-neuroinvasive arboviral illnesses.¹⁹ Before the position statement, CDC recommended voluntary WNF reporting by state and city/county health departments. A surveillance case definition also had been recommended for these public health jurisdictions in 2003 by CDC, but was not adopted by CSTE until after the position statement in 2005.¹⁹

We conducted a retrospective analysis to provide a baseline assessment of the completeness of WNF testing, confirmation, and reporting (collectively called ascertainment hereafter) among U.S. jurisdictions from 2003 through 2005. We introduce below a WNV syndrome ascertainment ratio to assess the completeness of WNF ascertainment relative to WNND at the jurisdiction level. The use of this relative measure reflects the national variability in WNF ascertainment that resulted from the varying policies, practices, and capacities of state health departments' laboratory and epidemiology programs, which in turn were responses to the aforementioned ascertainment challenges that occurred early in the epidemic. Notably, ratio indicators for evaluating surveillance sensitivity have been previously introduced²⁰ and applied to sexually transmitted diseases²¹ and polio eradication,²² but this is the first use of a WNV syndrome ascertainment ratio. Our assessment method is distinct from familiar evaluations of reporting completeness, which are performed for diagnosed cases only.¹⁵ In evaluating completeness of WNF reporting, the number of undiagnosed cases that are ignored would be substantial because WNF is known to be significantly underdiagnosed. Instead, the syndrome ascertainment ratio addresses undiagnosed cases by indirectly estimating the overall completeness of WNF surveillance. The observed relative frequencies of cases with febrile and neuroinvasive disease, which have all been ascertained, can be compared among jurisdictions and compared with expected relative syndrome frequencies. Because laboratory testing and public health surveillance rely on healthcare systems in which racial and ethnic disparities in access to care and diagnostic services are prevalent, the extent of differential WNF ascertainment among Blacks and Hispanics relative to non-Hispanic Whites is also estimated.

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MATERIALS

We designed parallel, voluntary surveys to solicit data from U.S. health departments and public health laboratories. Instructions designated January 1, 2003 through December 31, 2005 as the study period and questionnaires referenced WNV laboratory testing and surveillance-related policies and practices each year (Supplemental Appendices 1 and 2, available at www.ajtmh.org). During November and December 2006, questionnaires were e-mailed to 103 public health laboratory directors and arboviral surveillance coordinators in 52 state or large city/county health department jurisdictions (Houston, Los Angeles, New York City, Philadelphia, and Washington, DC) where human WNV cases had been reported during the study period.

Restrictions on specimen acceptance and WNV-specific, IgM-capture enzyme-linked immunosorbent assay testing in public health laboratories were assessed by reviewing guidelines provided by survey participants and health department websites. Documents were parsed into six testing restrictions: presence of neuroinvasive disease, hospitalization, certain patient ages, calendar date ranges, epidemiology program approval, and health department contact prior to specimen submission. Existing data from previous surveys (cited here) of public health laboratory practices, services, and capacities (2002–2004)²³; epidemiology and WNV surveillance capacities (2004)^{24,25}; and structures and functions of state public health agencies (2001)^{26,27} were also included in the analyses to augment data from the primary survey. These supplemental survey data were analyzed in relation to combined surveillance data for the three-year study period only.

Final reports of human WNV cases with illness onset dates from January 1, 2003 through December 31, 2005 were provided by CDC and the ArboNet surveillance system. Records with an unknown or other clinical syndrome were excluded (2.6%). For the study, race and ethnicity were categorized as Black, Hispanic, or non-Hispanic White. Records of other race/ethnicity groups, which appeared infrequently in the data (<2.0% each), were omitted because data were insufficient for their specific analysis. The final surveillance dataset included 14,584 records.

METHODS

We performed two types of analysis. First, we calculated a WNV syndrome ascertainment ratio (WNF/WNND) using counts of reported cases' syndromes for years and jurisdictions with at least one case each of WNF and WNND. The numerator and denominator of the ratio include symptomatic infections that are categorized clinically as either fever (without neuroinvasive disease) or neuroinvasive disease, respectively. This summary indicator is comparable to an incidence ratio for known cases. In characterizing the completeness of WNF ascertainment among health department jurisdictions and their regions, the syndrome ascertainment ratio is crude; it does not account for geographic differences in WNV ecology or the virulence of predominant strains. The ratio also assumes that WNND ascertainment variability is negligible relative to the degree of variability in WNF ascertainment. This assumption is tenable because of the varying policies, practices, and capacities of WNV programs and the ascertainment challenges described above. Symptom and serologic data from a New

York City neighborhood-based study conducted in 1999 established that as many as 30 WNF cases occur for every WNND case during an epidemic in a susceptible population.¹ By comparison, health departments' surveillance systems ascertained between 0.1 and 9.0 WNF cases for each WNND case from 2003 through 2005.⁸

A cutpoint of 1.0 was used to dichotomize the observed syndrome ascertainment ratios and assess jurisdiction-level, programmatic factors associated with more complete (≥ 1.0) or less complete (< 1.0) relative WNF ascertainment. This cutpoint is approximately the mid-point of jurisdictions' syndrome ratios during the study period and provides a reference value that is both intuitive and conservative for a baseline assessment of ascertainment performance; the value is not based on biology, clinical considerations, or any precedent in the literature. Because WNV activity and programs' capacities, policies, and practices may have varied over time, program correlates of ascertainment were assessed each year and for 2003–2005 combined. In the univariate analyses of syndrome ascertainment ratios and programmatic factors, odds ratios (ORs) and 95% confidence intervals (CIs) are reported together with Fisher's exact tests for the contingency tables. An alpha level < 0.05 defined significance.

In the second type of analysis, estimates of the differential WNF ascertainment among Blacks and Hispanics relative to non-Hispanic Whites were derived from multilevel regression models, which incorporate the variability in WNF ascertainment probability created at the level of autonomous programs and the syndrome variability at the case level (WNF versus WNND). Records with missing ethnicity (15%) or race and ethnicity (26%) data were included using multiple imputation to provide parameter estimates and associated uncertainty levels for the missing data (Supplemental Appendix 3, available at www.ajtmh.org).²⁸ Stepwise logistic regression models conditioned on all observed surveillance data (year, age group, sex, and syndrome) during imputation. County-level, U.S. Census data were added to the imputation models to generate plausible values of race (Black or White) and ethnicity (Hispanic or not). Census predictors of race and ethnicity were created from county-specific percentages of Blacks, Hispanics, and non-Hispanic Whites, which were calculated within strata defined by sex and 1 of 23 age groups and matched to each case's sex and age group. U.S. Census data for 2000 (Summary File 1) were obtained using DataFerret version 1.3.3 (Census Bureau/CDC) and linked to cases by using Federal Information Processing Standards county codes. Ten imputed datasets were created using IVEware (Imputation and Variance Estimation Software, University of Michigan).²⁹

By assigning different types of variation to the appropriate level of data aggregation, multilevel models fit the variability in WNF ascertainment at the case level and the jurisdiction level. The models predicted syndrome by using the odds of WNF ascertainment as the event of interest versus WNND ascertainment ($1 - \text{the probability of WNF}$). The logit link function $\eta_{ij} = \ln(\text{Pr}(\text{WNF}_{ij})/\text{Pr}(\text{WNND}_{ij}))$ and a Bernoulli sampling distribution were assumed for this binary syndrome outcome. Models were specific to each year or the overall study period. In each case, a random intercepts model with case-level predictors was initially fit (model 1), including fixed effects for age and the indicator covariates for sex, race, and ethnicity. A mixed-effects equation for the random intercepts model

with case-level predictors is $\eta_{ij} = \gamma_{00} + \gamma_{10} \times Age'_{ij} + \gamma_{20} \times Sex_{ij} + \gamma_{30} \times Race_{ij} + \gamma_{40} \times Ethnicity_{ij} + u_{0j}$, where i subscripts denote observations within jurisdictions, j subscripts are jurisdictions, and γ_{00} is the background log odds of WNF ascertainment. Other γ parameters are fixed effects for age (Age' to denote grand mean centering) and sex, race, and ethnicity indicator variable covariates; u_{0j} is a random effect that represents additional, unmodeled variability (error) in jurisdictions' log odds of WNF ascertainment. This mixed-effects model can also be expressed in a multilevel format as the system of equations Level 1: $\eta_{ij} = \beta_{0j} + \beta_{1j} (Age_{ij} - Age_{..}) + \beta_{2j} (Sex_{ij}) + \beta_{3j} (Race_{ij}) + \beta_{4j} (Ethnicity_{ij})$ and Level 2: $\beta_{0j} = \gamma_{00} + u_{0j}$.

Subsequent models included potentially significant, jurisdiction-level effects (generically as S_j) identified through univariate analyses of jurisdictions' syndrome ascertainment ratios, including U.S. Census region (West or Midwest versus Northeast or South) and population percentages of Blacks and Hispanics (both grand mean centered) (model 2). Additional parameters are also a function of β_{0j} , such that the reduction in u_{0j} is estimated when accounting for jurisdictions' WNV testing and surveillance policies/practices, U.S. Census region (West and Midwest versus Northeast and South), and population percentages of Blacks and Hispanics (both grand mean centered). To assess whether jurisdiction-level effects on WNF ascertainment probabilities vary with Black race or Hispanic ethnicity, cross-level interactions were also initially specified as functions of the jurisdiction-level predictors $\eta_{ij} = \gamma_{00} + \gamma_{10} \times Age'_{ij} + \gamma_{20} \times Sex_{ij} + \gamma_{30} \times Race_{ij} + \gamma_{40} \times Ethnicity_{ij} + \gamma_{01} \times S1_j + \dots + \gamma_{06} \times S6_j + \gamma_{31} \times S1_j \times Race_{ij} + \dots + \gamma_{36} \times S6_j \times Race_{ij} + \gamma_{41} \times S1_j \times Ethnicity_{ij} + \dots + \gamma_{46} \times S6_j \times Ethnicity_{ij} + u_{0j}$. In modeling race and ethnicity β terms as functions of the S_j predictors, a multilevel system of equations can be written as Level 1: $\eta_{ij} = \beta_{0j} + \beta_{1j} (Age_{ij} - Age_{..}) + \beta_{2j} (Sex_{ij}) + \beta_{3j} (Race_{ij}) + \beta_{4j} (Ethnicity_{ij})$ and Level 2: $\beta_{0j} = \gamma_{00} + \gamma_{01}(S1) + \dots + \gamma_{06}(S6) + u_{0j}$, $\beta_{1j} = \gamma_{10}$, $\beta_{2j} = \gamma_{20}$, $\beta_{3j} = \gamma_{30} + \gamma_{31}(S1) + \dots + \gamma_{36}(S6)$, and $\beta_{4j} = \gamma_{40} + \gamma_{41}(S1) + \dots + \gamma_{46}(S6)$.

Models were fit using restricted penalized quasi-likelihood estimation in *HLM 6* (Scientific Software International, Lincolnwood, IL). A t -ratio statistic was used for testing effects' significance.³⁰ Backward elimination of interaction terms and main effects identified parsimonious models. Adjusted odds ratios were averaged from the imputation datasets with variances for 95% confidence intervals incorporating variability in each dataset plus variability across the imputed datasets.²⁸ Institutional review board approval for the project was obtained from Emory University.

RESULTS

The highest syndrome ascertainment ratios, 8.97 in 2003 and 9.0 in 2004, occurred in jurisdictions with relatively large ($n = 1,935$) and small ($n = 20$) numbers of total cases, respectively. The cutpoint categorized 12 of 40 (30%) jurisdictions' ratios ≥ 1.0 in 2003, 17 (47%) of 36 ratios ≥ 1.0 in 2004, and 18 (44%) of 41 ratios ≥ 1.0 in 2005. Among 28 jurisdictions with syndrome ratios < 1.0 in 2003, 10 (24%) jurisdiction-specific and year-specific ratios were ≥ 1.0 either subsequent year. For 12 jurisdictions with a ratio ≥ 1.0 in 2003, most ratios remained at or above 1 (71%) but higher subsequent ratios were uncommon. The difference between the highest (9.0) and the lowest (0.1) ratios is a 90-fold difference in WNF ascertainment probabilities among jurisdictions.

WNV testing and reporting. Forty-seven laboratory surveys were completed (response rate = 90%). The surveys were most often completed by laboratory directors (28%) or section supervisors/managers (66%). Persons reporting front-line epidemiology (41%), management/supervisory (41%), or state epidemiologist (10%) functions completed 41 surveillance-related questionnaires (response rate = 79%). Thirty-five health department jurisdictions (63%) completed both surveys. The distributions of survey completion were relatively similar among jurisdictions after stratifying by population size in 2000, cerebrospinal fluid testing rates for WNV, WNND incidence, and WNV syndrome ascertainment ratio.

In 2003, WNV syndrome ascertainment ratios were ≥ 1.0 in 38% of jurisdictions that encouraged healthcare providers to submit suspect WNF cases' specimens to a public health laboratory. No jurisdictions that either encouraged specimen referral solely to private laboratories or did not promote WNF testing had a syndrome ascertainment ratio ≥ 1.0 (OR = undefined) (Table 1). Syndrome ascertainment ratios < 1.0 were generally more common among jurisdictions requiring the presence of neuroinvasive disease, hospitalization, certain patient ages, calendar date ranges, epidemiology program approval, or health department contact prior to specimen submission. Syndrome ascertainment ratios were more likely ≥ 1.0 in jurisdictions with 1 or none of these testing restrictions (2003–2005: OR = 7.7, 95% CI = 1.3–46.4, $P = 0.04$).

Each year, WNV testing by public health laboratories was typically ($\geq 83\%$) free of charge for all patients and, with one exception, testing charge policies did not change each year. The WNV syndrome ascertainment ratios were not associated with free testing by public health laboratories or provision of free specimen shipping or shipping and containers in any year. Syndrome ascertainment ratios were less likely ≥ 1.0 in jurisdictions where commercial WNV testing was available locally compared with jurisdictions that indicated commercial testing was not yet being performed locally in 2003 (OR = 0.2, 95% CI = 0.0–0.9, $P = 0.09$). Positive specimens from commercial laboratories frequently were confirmed for case counting, but this practice was unassociated with jurisdictions' syndrome ascertainment ratios and decreased over time (2003: 84%, 2004: 76%, 2005: 67%). The estimated percentage of probable or confirmed cases reported through testing outside the public health laboratory system increased in 2005 to a median of 21% of cases (interquartile range [IQR] = 71) from a median of 13–14% in the two previous years (2003: IQR = 40, 2004: IQR = 25). In 2005, jurisdictions with a syndrome ascertainment ratio ≥ 1.0 were almost seven times more likely to receive at least 50% of WNV case reports from outside testing (OR = 6.8, 95% CI = 1.3–34.6, $P = 0.04$) when compared with jurisdictions receiving most reports from tests with positive results performed by public health laboratories within the jurisdiction.

By 2006, all but two epidemiology programs (95%) indicated that laboratories were legally required to report WNV positive test results in their jurisdictions and 80% of jurisdictions legally required reporting of WNV positive tests from specimens collected within the jurisdiction but tested by out-of-state laboratories. Most programs (80%) had also designated WNF reportable in their jurisdictions by 2006. Syndrome ascertainment ratios were not significantly associated with establishment of WNV-positive test results as laboratory reportable, requiring reporting of positive test results from

TABLE 1

Public health laboratories' policies and practices for West Nile virus testing and West Nile fever ascertainment completeness by year, United States, 2003–2005

Policy/practice	No. (%) of jurisdictions by WNV syndrome ascertainment ratio*					
	2003		2004		2005	
	≥ 1.0	< 1.0	≥ 1.0	< 1.0	≥ 1.0	< 1.0
Promote WNF tests†						
Public laboratory	9 (38)	15 (63)	8 (40)	12 (60)	12 (57)	9 (43)
None/private only	0	9 (100)	4 (50)	4 (50)	3 (27)	8 (73)
Test restrictions‡						
1 or none	9 (56)	7 (44)	9 (69)	4 (31)	10 (71)	4 (29)
2 or more	2 (14)	12 (86)	6 (38)	10 (63)	6 (32)	13 (68)
Testing charges						
Free for all patients	8 (30)	19 (70)	10 (48)	11 (52)	11 (42)	15 (58)
Sometimes/not free	4 (57)	3 (43)	6 (75)	2 (25)	5 (63)	3 (38)
Commercial tests§						
Available locally	5 (25)	15 (75)	15 (58)	11 (42)	15 (48)	16 (52)
Not available locally	6 (67)	3 (33)	1 (100)	0	1 (100)	0
Laboratory confirmation						
Required	10 (37)	17 (63)	10 (48)	11 (52)	8 (36)	14 (64)
Not required	2 (40)	3 (60)	6 (75)	2 (25)	8 (67)	4 (33)
Outside testing¶						
50% or more	2 (40)	3 (60%)	2 (33)	4 (67)	9 (69)	4 (31)
Less than 50%	5 (22)	18 (78%)	8 (44)	10 (56)	4 (25)	12 (75)
Total	12 (30)	28 (70%)	17 (47)	19 (53)	18 (44)	23 (56)

*The West Nile virus (WNV) syndrome ascertainment ratio is the year- and jurisdiction-specific ratio of case counts of each disease syndrome: West Nile fever (WNF)/West Nile neuroinvasive disease. The ratio was calculated for jurisdictions with ≥ 1 febrile and neuroinvasive case each year (2003: 40, 2004: 36, and 2005: 41).

† Promoted tests of suspect WNF cases in periods of WNV activity by encouraging specimen submission to public health laboratory or public and private laboratories vs. submission to private laboratories only or not promoted.

‡ Six WNV testing restrictions are hospitalization, neuroinvasive disease, certain ages, calendar date ranges, epidemiology program approval, and health department contact prior to specimen submission.

§ Commercial laboratory testing for WNV performed for at least some patients in the jurisdiction.

|| Require confirmation of positive results from commercial laboratories to count a case of WNV disease.

¶ Year-specific percentage of confirmed/probable cases reported via tests outside the jurisdiction's laboratory system.

out-of-state laboratories, or including WNF in lists of reportable diseases in any year (Table 2).

Among eight jurisdiction-wide activities to enhance WNV reporting, dissemination of advisories/recommendations (92%), surveillance manuals/protocols (74%), or newsletters/other periodicals (62%) or conducting training/seminars on WNV reporting for clinicians (64%) were commonly reported. Less often, health departments established electronic laboratory reporting (41%), periodically contacted reporting sources by telephone to inquire about cases (31%), or conducted retrospective WNV case finding through laboratory or medical record reviews (3%). For the three-year study period, a syndrome ascertainment ratio ≥ 1.0 was more likely in jurisdictions that conducted training/seminars (OR = 10.0, 95% CI = 1.1–89.8, *P* = 0.04) and more likely in jurisdictions that performed four or more surveillance activities (OR = 11.8, 95% CI = 1.3–107.4, *P* = 0.03).

For the three-year period, no significant association was observed (*P* = 0.7) between the syndrome ascertainment ratio and technical/analytic staffing in public health laboratories, measured as staffing rates greater than 3.0 filled, full-time equivalent (FTE) positions per 100,000 residents compared with jurisdictions with lower staffing rates. When FTE rates were calculated for surveillance staff, three-year syndrome ascertainment ratios ≥ 1.0 were six times more likely in health departments with FTE rates ≥ 5.0 WNV-dedicated staff per one million residents (OR = 6.4, 95% CI = 1.0–40.3, *P* = 0.1) and four times more likely with infectious disease staff rates ≥ 5.0 per one million residents (OR = 4.5, 95% CI = 1.1–19.4, *P* = 0.08) compared with jurisdictions with lower staffing rates.

Multilevel WNF ascertainment. In multilevel analyses, WNF ascertainment was independently associated with each of the four case-level characteristics (age, sex, race, and ethnicity), and these associations were relatively unaffected either by stratifying by year or by the addition of select, jurisdiction-level predictors (Table 3). The odds of WNF ascertainment relative to WNND ascertainment decreased by 0.02 for each year of age beyond the mean age (49 years) of all cases (2003–2005: OR = 0.98, 95% CI = 0.97–1.0, *P* = 0.03). When compared with non-Hispanic Whites, the odds of WNF ascertainment were lower among Blacks (2003–2005: 0.56, 95% CI = 0.31–0.99, *P* = 0.05). In 2005, the likelihood of WNF ascertainment among Blacks was 60% lower in jurisdictions where most (> 50%) case reports were received from WNV testing outside the public health laboratory system (OR = 0.40, 95% CI = 0.18–0.90, *P* = 0.03) compared with non-Hispanic Whites. However, the likelihood of WNF ascertainment among Blacks did not differ from non-Hispanic Whites in jurisdictions where a minority of reports were received from outside testing in 2005 (OR = 0.86, 95% CI = 0.58–1.29, *P* = 0.47). The likelihood of WNF ascertainment among Hispanics was 31% lower relative to non-Hispanic Whites (2003–2005: OR = 0.69, 95% CI = 0.48–0.98, *P* = 0.04).

DISCUSSION

We used a WNV syndrome ascertainment ratio, the ratio of WNF case counts over WNND counts, to characterize the completeness of WNF ascertainment in the United States from 2003 through 2005. Policies, practices, and capacities of health departments' epidemiology and laboratory programs

TABLE 2

Public health surveillance policies and practices for West Nile virus testing and West Nile fever ascertainment completeness by year, United States, 2003–2005

Policy/practice	No. (%) of jurisdictions by WNV syndrome ascertainment ratio*					
	2003		2004		2005	
	≥ 1.0	< 1.0	≥ 1.0	< 1.0	≥ 1.0	< 1.0
Laboratory reportable†						
Yes	6 (29)	15 (71)	9 (47)	10 (53)	10 (38)	16 (62)
No	0	6 (100)	1 (25)	3 (75)	1 (100)	0
Out-of-state reports‡						
Yes	9 (33)	18 (67)	10 (48)	11 (52)	13 (48)	14 (52)
No	0	6 (100)	2 (29)	5 (71)	2 (40)	3 (60)
WNV reportable‡						
Yes	3 (22)	11 (79)	6 (40)	9 (60)	7 (35)	13 (65)
No	2 (25)	6 (75)	3 (50)	3 (50)	3 (100)	0
Peak year						
Current	9 (41)	13 (59)	1 (33)	2 (66)	4 (100)	0
Past	3 (18)	14 (82)	14 (47)	16 (53)	14 (38)	23 (62)
Enhance surveillance‡						
≥ 4 activities	7 (41)	10 (59)	11 (58)	8 (42)	13 (65)	7 (35)
≤ 3 activities	2 (13)	14 (88)	1 (11)	8 (89)	2 (17)	10 (35)
Total	12 (30)	28 (70)	17 (47)	19 (53)	18 (44)	23 (56)

*The West Nile virus (WNV) syndrome ascertainment ratio is the year- and jurisdiction-specific ratio of case counts of each disease syndrome: West Nile fever (WNV)/West Nile neuroinvasive disease. The ratio was calculated for jurisdictions with ≥ 1 febrile and neuroinvasive case each year (2003: 40, 2004: 36, and 2005: 41).

† Legal requirements for reporting of WNV-positive laboratory results, WNV-positive results from specimens collected in state but tested out-of-state, and reporting of WNF each designated by May of year.

‡ Eight surveillance activities realized jurisdiction-wide in the study period are dissemination of advisories/recommendations, surveillance manuals/protocols, or newsletters/other periodicals; conducting training/seminars on WNV reporting for clinicians; establishing electronic laboratory reporting; telephoning reporting sources periodically; and conducting retrospective case finding through laboratory or hospital record reviews.

were linked to syndrome ascertainment ratios for their jurisdictions. These univariate analyses identified commercial testing unavailability (2003), fewer restrictions on WNV testing by the health department laboratories (2003 and 2005), four or more health department surveillance activities to enhance reporting (2004 and 2005), and receipt of most case reports from testing outside the public health laboratory system (2005) as potentially related to increased WNF ascertainment. Although chance findings are possible, the timing of these significant policies and practices are consistent with the changing laboratory and surveillance capacities of health departments' laboratory and epidemiology programs and the overall response to the emergence of WNV in the United States. For example, commercial enzyme immunoassay availability would be expected to be most significantly related to WNF ascertainment in 2003 when a market for the tests was initially being established. Other year-specific inconsistencies, especially the lack of measurable significance for the effects of fewer restrictions on WNV testing by the health department laboratories in 2004 and surveillance activities to enhance reporting in 2003, are likely explained by the small numbers of jurisdictions in the analyses. Although survey response rates were not optimal, response rates did not differ when stratified by population size, cerebrospinal fluid testing rates for WNV, WNND incidence, or the syndrome ascertainment ratio itself.

Because of the potential severities of WNV-related febrile illness and its sequelae,^{2–6} there is a need for an accepted measure of WNF surveillance sensitivity. Ratio indicators for evaluating surveillance sensitivity have been previously introduced and applied,^{20,22} but this study is the first use of a WNV syndrome ascertainment ratio. Its application provided a simple and effective measure of the relative frequency of observed syndromes among states and large city/county public health programs, enabling sources of WNF ascertainment variability to be identified each year. Importantly, we specifically refer to

the relative completeness of ascertainment because all cases included in these analyses had to have been tested, confirmed, and reported regardless of syndrome. However, among the unknown cases not included in the dataset (i.e., cases not ascertained), the syndrome ascertainment ratio is not intended to determine the frequency or number of cases that were untested, tested but unconfirmed, or tested and confirmed but not reported. Instead, the effectiveness of measuring the relative frequency of observed syndromes across jurisdictions or subpopulations depends on two assumptions. First, WNND ascertainment is assumed to be stable because testing, confirmation, and reporting are relatively complete. Persons with WNND are likely to be hospitalized (> 90%) because of disease severity,⁴ but the proportion of people with WNND who are diagnosed as having WNV infection is unknown. A meningitis or encephalitis clinical manifestation should raise the index of suspicion, particularly during seasonal or epidemic WNV and in the context of increasing publicity about WNV, making etiologic diagnosis of WNND more likely than WNF. Although CSTE has described WNND reporting as reasonably complete,¹⁹ we did not find any published studies of the completeness of WNND or WNV reporting. Second, WNF ascertainment varies, but persons with symptomatic, febrile illness are eligible for ascertainment because healthcare is sought and WNV infection is considered in the differential diagnosis. Estimates of the proportion of persons with WNF seeking healthcare or requiring hospitalization vary, but are substantial.^{1–4,31}

Our estimates of the reduced likelihoods of WNF ascertainment among Blacks and Hispanics relative to non-Hispanic Whites should be interpreted cautiously because a significant portion of the race data (26%) and the ethnicity data (41%) were missing. Ignoring records with missing data would have substantially reduced our sample size and would have assumed that data are missing completely at random, which is unlikely.

TABLE 3

Multilevel models of West Nile virus disease syndrome using case-level demographics and jurisdiction-level policies, practices, and capacities by year, United States, 2003–2005*

Characteristic	2003	2004	2005	2003–2005
No. of cases (no. jurisdictions)				
Model 1	9,282 (40)	2,305 (36)	2,635 (41)	14,353 (48)
Model 2	7,763 (21)	1,821 (27)	1,110 (23)	9,098 (22)
Intercept (u_{0j}) variance component (standard deviation)†				
Model 1	1.12 (1.06)	0.97 (0.98)	0.54 (0.73)	0.79 (0.89)
Model 2	0.16 (0.40)	0.53 (0.73)	0.38 (0.62)	0.28 (0.53)
Adjusted odds ratios (95% confidence intervals)				
Case-level demographics‡				
Age, years§				
Model 1	0.98 (0.97–0.98)	0.98 (0.98–0.99)	0.98 (0.98–0.9)	0.98 (0.98–0.98)
Model 2	0.98 (0.97–0.98)	0.98 (0.98–0.99)	0.98 (0.97–0.99)	0.98 (0.97–1.0)
Female				
Model 1	1.30 (1.20–1.42)	1.36 (1.19–1.56)	1.06 (0.80–1.40)	1.25 (1.15–1.36)
Model 2	1.27 (1.16–1.38)	1.36 (1.19–1.57)	0.87 (0.61–1.23)	1.19 (1.0–1.41)
Black†				
Model 1	0.51 (0.34–0.76)	0.39 (0.22–0.7)	0.58 (0.42–0.81)	0.52 (0.42–0.65)
Model 2	0.47 (0.22–1.02)	0.39 (0.21–0.73)	0.86 (0.58–1.29¶)	0.56 (0.31–0.99)
Hispanic†				
Model 1	0.74 (0.64–0.86)	0.68 (0.51–0.91)	0.57 (0.43–0.75)	0.67 (0.59–0.77)
Model 2	0.72 (0.61–0.86)	0.62 (0.45–0.86)	0.65 (0.28–1.50)	0.69 (0.48–0.98)
Jurisdiction-level policies, practices, and capacities (model 2 only)‡				
Available commercial tests	0.32 (0.21–0.51)	–	–	–
One or no testing restrictions	0.90 (0.48–1.68)	–	1.0 (0.47–2.10)	1.33 (0.62–2.86)
Majority reports by outside testing¶	–	–	Black: 0.40 (0.18–0.89); White: 1.72 (0.85–3.46)	
≥ 4 surveillance activities	–	2.96 (1.76–5.00)	2.62 (1.52–4.51)	1.35 (0.68–2.72)
≥ 5.0 infectious disease staff per million residents	–	–	–	2.04 (0.86–4.81)
Census data (model 2 only)				
Western regions	2.04 (1.08–3.86)	1.98 (0.88–4.48)	1.65 (0.61–4.43)	1.63 (0.72–3.68)
% Black§	0.97 (0.94–1.0)	0.99 (0.96–1.02)	0.99 (0.96–1.02)	0.99 (0.95–1.03)
% Hispanic§	0.98 (0.97–0.99)	1.00 (0.98–1.03)	1.01 (0.97–1.04)	1.02 (0.98–1.06)

* Model 1 has a random intercepts and case-level predictors only; model 2 adds jurisdiction-level predictors and significant, cross-level interactions. Models predict syndrome and the odds of WNF is the event of interest (vs. WNND as the reference group).

† Model estimates account missing race and ethnicity data via multiple imputation (see text).

‡ Jurisdiction-level characteristics were included in year-specific models when potential significance was identified through univariate analyses of jurisdictions' syndrome ascertainment ratios (see text for description).

§ Age, % Black, and % Hispanic centered.

¶ For Blacks in jurisdictions with < 50% reports by outside testing only (i.e., interaction modeled).

Instead, missing data uncertainty was appropriately represented by generating multiple, analogous datasets in which imputed race and ethnicity vary. The surveillance data were augmented for imputation by using county-level race and ethnicity data from the U.S. Census. The underlying assumption that racial and ethnic composition of an area likely correlates with one's own race and ethnicity is supported by the realities of U.S. neighborhood racial segregation.³² Multiple imputation also assumes that the extent to which data are missing is statistically independent of one's own race or ethnicity after accounting for the remaining fully observed data (i.e., data are missing at random). In these analyses, this assumption was presupposed because it is impossible to validate without supplemental data.³³ More complicated adjustments are possible, but require more detailed, problem-specific statistical development and would not be available in standard software.

Given the overall health disparities, specific disparities in infectious diseases rates, and disparate healthcare among racial and ethnic minorities,^{34–36} the possibility that WNF ascertainment was 44% less frequent among Blacks and 31% less frequent among Hispanics relative to non-Hispanic Whites, after accounting for missing data uncertainty and

program-level sources of ascertainment variability, is worrisome. Specifically, we found that testing and reporting between Blacks and non-Hispanic Whites was unequal only when most reports originated from outside the public health laboratory system in 2005. This finding suggests that differential accessibility and use of commercial tests may play a role in the inequality. Also, the combined effects of residency in regions where WNF ascertainment was less rigorous, together with higher population percentages of Blacks in those areas, may create more missed opportunities for WNF ascertainment in Blacks. In 2003, WNF ascertainment was twice as likely in West and Midwest regions compared with Southern and Northeast regions. All eight states with ≥ 20% of the population comprised of Blacks were in the Southern region, and two-thirds of jurisdictions with 10–20% Black residents were in Southern or Northeast regions. Hispanic population percentages were more evenly distributed among regions (jurisdictions with ≥ 15% Hispanic residents were located in Southern [19%], Northeast [25%], Midwest [19%], and Western [38%] regions).

Other factors might also explain the racial and ethnic disparities in WNF ascertainment we observed. A study of 172 WNV cases that were hospitalized in Houston determined that attack

rates were relatively similar for Blacks (5.7 per 100,000) and non-Hispanic Whites (6.6 per 100,000), but substantially lower in Hispanics (3.5 per 100,000).³⁷ One explanation for this finding is that prior flavivirus exposure among Hispanics creates an increased frequency of cross-protective antibodies, which could mitigate WNV disease severity. Nevertheless, additional research and program evaluation are needed to explain these observed differences by directly investigating their underlying mechanisms. In particular, active case-finding could produce a representative cohort of case-patients for such analyses. Collectively, reduced ascertainment and incomplete race/ethnicity data³⁸ undermine surveillance objectives to monitor disease in populations that often have the greatest risk.³⁹

This baseline analysis of WNF ascertainment completeness demonstrated that multilevel analyses can provide estimates of the relative importance of multiple sources of ascertainment variability. Previous evaluations have established that reporting completeness varies,¹⁵ but surveillance ascertainment variability had not been jointly measured at the individual and public health systems levels. We identified availability of laboratory testing in the public domain, active surveillance, and surveillance staffing rates as program characteristics that are particularly associated with successful WNF ascertainment. We also found that ascertainment variability was associated with surveillance and infectious disease control staffing rates (2003–2005), Census regions (2003), and population percentages of Blacks and Hispanics (2003). These findings not only suggest that improvements in monitoring human disease can be achieved by agencies operating at optimal capacities, but also reinforce concerns raised about decreased federal funding for prevention and control of WNV and other emerging infectious diseases.

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Note: Supplemental appendices are available at www.ajtmh.org.

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