Can We Prevent Epidemics of West Nile Encephalitis?

Internal Medicine Ground Rounds
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This is to acknowledge that Robert W. Haley, MD has disclosed that he does not have any financial interests or other relationships with commercial concerns related directly or indirectly to the program. Dr. Haley will not be discussing off-label uses in his presentation.

Biographical Information:

Robert W. Haley, M.D., is Professor of Internal Medicine, holder of the Distinguished Chair in Medical Research Honoring America's Gulf War Veterans, endowed by Ross Perot and the Perot Foundation, and heads the Division of Epidemiology. In addition to teaching a course in epidemiology for the clinical investigator and SAS computing for research in the Department of Clinical Science, his research currently focuses on the neurological and genetic basis for sarin-related Gulf War illness and the possible role of paraoxonases in coronary atherosclerosis and congestive heart failure, and he leads the Texas Medical Association's clean air policy development. While in medical school, Dr. Haley worked in Dr. James Luby's virology laboratory on an epidemiologic study that demonstrated continuing transmission of arboviruses in Dallas County. Recently he rekindled that interest with a collaborative analysis of the 2012 West Nile virus (WNV) epidemic that appeared in *JAMA* and forms the starting point for this grand rounds presentation.

Purpose and Overview:

After briefly reviewing the clinical features and what is known of the causes of WNV epidemics relevant to prevention, the presentation will explain the practice of mosquito trap surveillance and the calculation of the vector index and demonstrate its power to predict human epidemics with 3-4 weeks lead time before human cases and deaths begin increasing. This lead time raises the possibility of community-wide intervention with aerial spraying of insecticides, which has been shown effective in quelling WNV epidemics. Obstacles to implementing preventive measures are the need for political approval for interventions and public concerns over the immediate and long-term adverse effects of insecticides on humans, fetuses, large flying insects and the environment. Thus, the opportunity for effective prevention afforded by the vector index is complicated by the politics of ordering aerial insecticide spraying before the appearance of human cases and deaths.

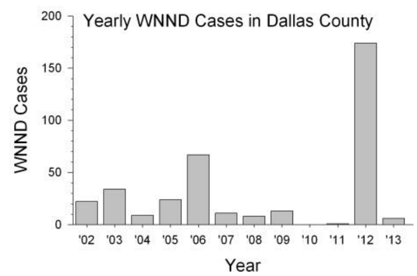
Educational Objectives:

1. Review the clinical features and causes of WNV epidemics relevant to prevention.
2. Learn how health departments perform mosquito trap surveillance and calculate the species-specific mosquito vector index.
3. Explore how the vector index predicts large human epidemics of WNV encephalitis and the amount of lead time it provides for intervention.
4. Understand the evidence regarding public concerns over aerial insecticide spraying.
5. Struggle with the political dilemma of ordering intervention before human cases and deaths appear.

Dr. Haley acknowledges the important contributions of County Epidemiologist Dr. Wendy Chung and her epidemiologic staff and Dr. James Luby, for 5 decades the driver of Dallas' WNV surveillance and control efforts. Any errors, however, are his own.

Introduction

West Nile virus (WNV) infection is a serious threat, causing fever in 20% and neurological deficits, often long-lasting or permanent, in 1 of 250.[1] It first came to the Americas in 1999 when cases of West Nile neuroinvasive disease (WNND) and West Nile fever (WNF) were reported in New York City.[1] Over the subsequent 5 years it spread sequentially westward until, by 2003, it had become endemic in all 48 contiguous states. Moderately sized epidemics occurred into the middle of the 2000 decade and thereafter progressively declined, except in certain more highly affected urban areas such as Sacramento, Tucson, Houston, and parts of Louisiana and Florida. An 11 year analysis showed that WNV infection first appeared in Dallas in 2002, with the first substantial epidemic, with 67 WNND cases, in 2006 (*figure*).[2] The annual incidence thereafter fell progressively until only one WNND case occurred in all of 2010 and 2011, reflecting declining incidence throughout the country.[1]



In 2012 the incidence of WNV infection dramatically increased throughout the country, and the largest urban epidemic occurred in Dallas County and the surrounding counties of Tarrant, Collin and Denton counties.[3] Dallas recorded 173 cases of WNND and 21 deaths (*figure*). Because of the long history of arboviral epidemic problems in Dallas and the long-term interest by UT Southwestern's virologist Dr. James Luby,[4] surveillance of mosquito and human infections have been systematically conducted every year by the municipal and county health departments in the Dallas area. When the number of human WNND cases and deaths dramatically increased in late July 2012, Dr. Luby and a group of infectious disease specialists from around the city recommended aerial spraying of insecticides to quell the epidemic, as had been done for the first time in an urban area in Dallas County in 1966.[5] Following public protests by an anti-insecticide interest group and political opposition in the County government, the Dallas County Judge in his position as head of the emergency response authority ordered immediate aerial spraying, and the epidemic soon dissipated.

In the succeeding months, because of the unusually large number of WNND cases and the unusually complete mosquito and human surveillance data dating back to the introduction of WNV, a collaborative team from UT Southwestern and the epidemiology unit of Dallas County Health and Human Services (DCHHS) conducted an investigation of the Dallas County epidemic, and arboviral experts from the Centers for Disease Control and Prevention (CDC) Vector-Borne Diseases Division at Ft. Collins, Colorado, investigated the impact of aerial spraying in the four county region around Dallas. Subsequently the Dallas County Judge held a meeting for the anti-insecticide interest groups to present their concerns and evidence, to which UT Southwestern faculty responded. The following is a summary of findings and conclusions relevant to prevention of WNND cases and deaths in future WNV epidemics in Dallas.

Features of WNV Epidemics Relevant to Prevention

Relevant Clinical Features of WNV Infection

Epidemiologic surveillance of WNV epidemics generally focuses primarily on WNND cases, augmented by reports of positive blood donors from regional blood banks and reports of WNV-associated deaths, because virtually all of these are discovered and potentially reported. WNF cases are generally not considered because their diagnosis and reporting are so heavily influenced by awareness in the public and among physicians, which rises with news reporting of epidemics.[6]

The interval from infecting mosquito bite to reporting of WNND cases to the local health department is a central characteristic of WNV epidemic control.[2] The average duration from infecting mosquito bite to first symptom of WNND is one week; it then takes an average of one week for symptoms to become severe enough for hospitalization, and another week for the diagnostic evaluation, confirmatory WNV serological testing and reporting to the health department. The testing and reporting step was prolonged by another few days in the first half of the Dallas 2012 epidemic until the presence of an epidemic was widely appreciated. Consequently, there is generally a 3-4 week interval between infecting mosquito bite and reporting of WNND cases to the local health department to be considered in decision-making.

Causes of WNV Epidemics

Human WNV epidemics occur when bird-mosquito epizootic's increase in size until they begin spilling over into humans.

The Vector. In the United States, although many species of mosquitoes may occasionally serve as bridge vectors transmitting WNV to humans, most urban infections are transmitted by the common house mosquito, *Culex quinquefasciatus*; while infections in rural environments tend to be transmitted by *Culex tarsalis*.

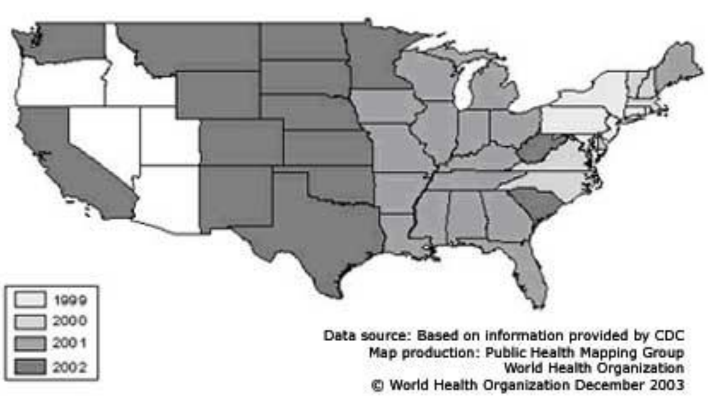
Culex quinquefasciatus breeds aggressively in even the smallest water sources around urban houses, such as bottle caps, French drains, overwatered lawns and birdbaths, as well as neglected swimming pools and abandoned tires. This makes it extremely difficult to reduce their numbers by early season preventive measures.

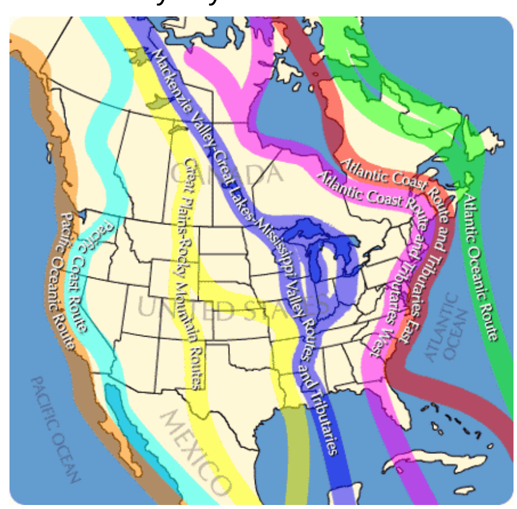
Female *Culex* mosquitoes may live all summer, and some, even WNV-infected ones, survive the winter in protected environments. Eggs survive the winter to hatch in early spring, and WNV-infected female *Culex* may pass the virus to their eggs which then hatch as infected mosquitoes (vertical transmission).

Culex quinquefasciatus are "canopy dwellers"[7]; that is, at any moment, 80% are found near the tops of trees where they feed on birds, while the remaining 20% are circulating down to the ground to lay eggs and feed on mammals. This suggests that aerial spraying of insecticides might be more effective in reducing numbers of *Culex* than ground spraying.

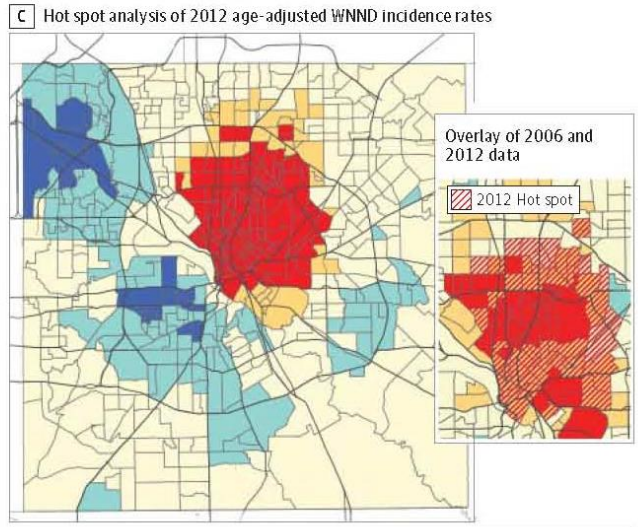
Culex quinquefasciatus remain near their breeding site throughout life; whereas, the more rural *Culex tarsalis* may range long distances, one possible explanation for the east to west spread of WNV across the U.S. and Canada from 1999 to 2003.

Possible Spread along Avian Flyways. Another suggested explanation for the westward spread of WNV is via the large bird populations migrating north from Central and South American to the U.S. and Canada in our spring and back again in our fall.[8] The year-by-year sectional pattern of spread of WNV across the U.S. from 1999 to 2003 (*figure below left*) corresponds to the 4 main avian migratory flyways over North America: the Atlantic, Mississippi, Central and Pacific (*figure below right*). This theory suggests that WNV spreads from one flyway to the next over our winter in Central/South America, so that the virus is introduced early the following spring by the migratory birds to our resident birds.





Recurrent Geographic Foci. Geospatial analysis showed that the both the 2006 and 2012 Dallas epidemics were focused in a "hot spot" centered over the Park Cities and North Dallas (*figure to right*), and smaller numbers of WNV cases occurring in the remaining years also occurred predominantly on the north side of the Trinity River.[2] A multivariable statistical analysis found that census tracts located in the 2012 hot spot were characterized by higher property values, greater housing density, and a higher percentage of unoccupied homes, but there was no difference in the area covered by water.[2] Thus, WNV infections tend to recur year after year in the same neighborhoods with the highest housing density. This may be due to the greater predominance of the common house mosquito in more densely housed neighborhoods.



Getis-Ord Gi* z scores greater than |2.0| were statistically significant ($P < .05$). A high and positive z score value indicates that a census tract is surrounded by other census tracts reporting high West Nile virus disease incidence (ie, part of a hot spot).

Weather. Dallas' two epidemic years, 2006 (67 WNND cases) and 2012 (173 WNND cases), differed from the non-epidemic years by having extremely warm winter and spring weather, the fewest hard freeze days, and the most rain interrupting the 6-year regional drought. Prior studies have associated WNV epidemics with both droughts and excessive rain, warmer winter, and early spring (reviewed by Chung[2]). These conditions favor overwintering of WNV-infected mosquitoes, earlier and greater mosquito abundance, and possibly more rapid viral proliferation.

Preexisting Immunity in Birds. Although the 2012 Dallas epidemic followed two years of unusually low numbers of human WNND cases (none in 2010 and 1 in 2011), over the prior 10 years the number of WNND cases each year was not associated with the number of cases the prior year. However, in 2013 Dallas had only 6 cases of WNND, a very small number, despite an extremely warm winter and an even larger mosquito abundance than in 2012. This suggests that a high rate of immunity in the Dallas bird population from the large 2012 epizootic might have prevented a repeat bird-mosquito epizootic in 2013.

A detailed study of WNV in Los Angeles from 2003 to 2011 by Kwan et al.[9] strongly supports the importance of antecedent immunity of the bird population in epidemic occurrence. In that study the yearly incidence of human WNND cases in July – September was inversely associated with the seroprevalence of WNV infection in house finches and house sparrows the preceding January-March (*Fig. 9 from Kwan et al*.[9]). Human epidemics did not occur until the avian immunity level declined to <10%—far less than the herd immunity in human populations of ~80% required to prevent epidemics of contagious diseases.

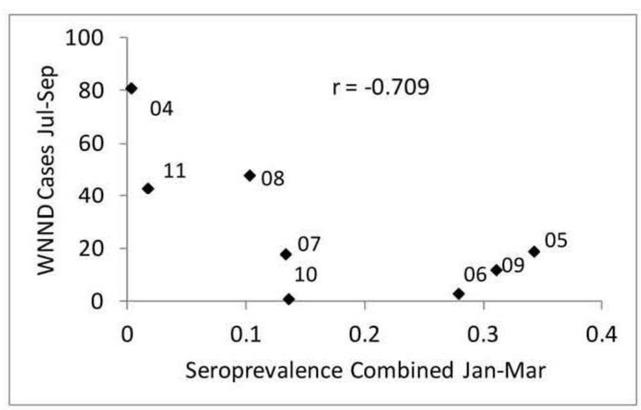


Figure 9. West Nile neuroinvasive disease (WNND) cases during July-September plotted as a function of combined antecedent House Finch and House Sparrow seroprevalence during January-March for each year from 2003-2011. Values were inversely correlated (r, $P<0.05$).

Mutation of the Virus. The WNV is an RNA flavivirus, prone to mutation. The strain that appeared in New York in 1999 had far greater epidemic potential and virulence than the strains spreading around Africa, Asia, the Middle East, the Mediterranean and Europe at least since the 1930s. The 1999 New York strain (designated NY99) resembled the Israeli strain. As WNV spread across the United States by 2002 it had mutated to a new genotype (designated North American WN02, or NA/WN02), which displaced NY99 because of it greater efficiency in disseminating in mosquito populations.[10] In 2005 a new WNV genotype (Southwest WN03, or SW/WN03) was identified in the Houston area.[10] New, as yet unpublished data suggest that the 2012 Dallas epidemic involved a new cluster (personal communication from Ward Wakeland), which will be discussed. Thus, the WNV appears to be continuously evolving by natural selection of new genotypes with greater epidemic potential and virulence.

Methods of Predicting Human Epidemics of WNV

Mosquito Trap Surveillance

Health departments estimate the ***mosquito abundance*** and the ***mosquito WNV infection rate*** by trapping mosquitoes, sorting out the *Culex quinquefasciatus* mosquitoes, counting them, and testing the batch for WNV.[6] Gravid traps, most often used, selectively trap female mosquitoes ready to lay eggs after a blood meal by attracting them with scents resembling stagnant water (e.g., grass clippings, rabbit chow, cow manure, fish oil, etc.). This preferentially attracts *Culex quinquefasciatus* and maximizes the likelihood of detecting virus.

Mosquito abundance = no. of Culex mosquitoes in a trap / no. of nights
(expressed as mosquitoes per trap night in the sampled area)

Minimum infection rate (MIR) = no. of WNV-positive batches / no. of batches tested
(assumes only 1 infected mosquito per batch, and ranges to ~30 per 1,000 mosquitoes, ~3%)

Maximum likelihood estimated (MLE) rate = more accurate estimate by CDC's Excel add-in[11]
(ranges to ~50 per 1,000 mosquitoes, or 5%)

The Species-Specific Mosquito Vector Index

Mosquito abundance predicts poorly when abundance is high but WNV is absent, and MLE mosquito infection rate predicts poorly when abundance is low but the MLE infection rate is high as with old mosquito populations which may have high WNV infection rates.

Consequently, the preferred statistic for predicting human epidemics is the vector index,[6] which appears to predict human epidemics accurately. The vector index (VI) is calculated for a given mosquito species by multiplying its abundance by its MLE infection rate:[12,13]

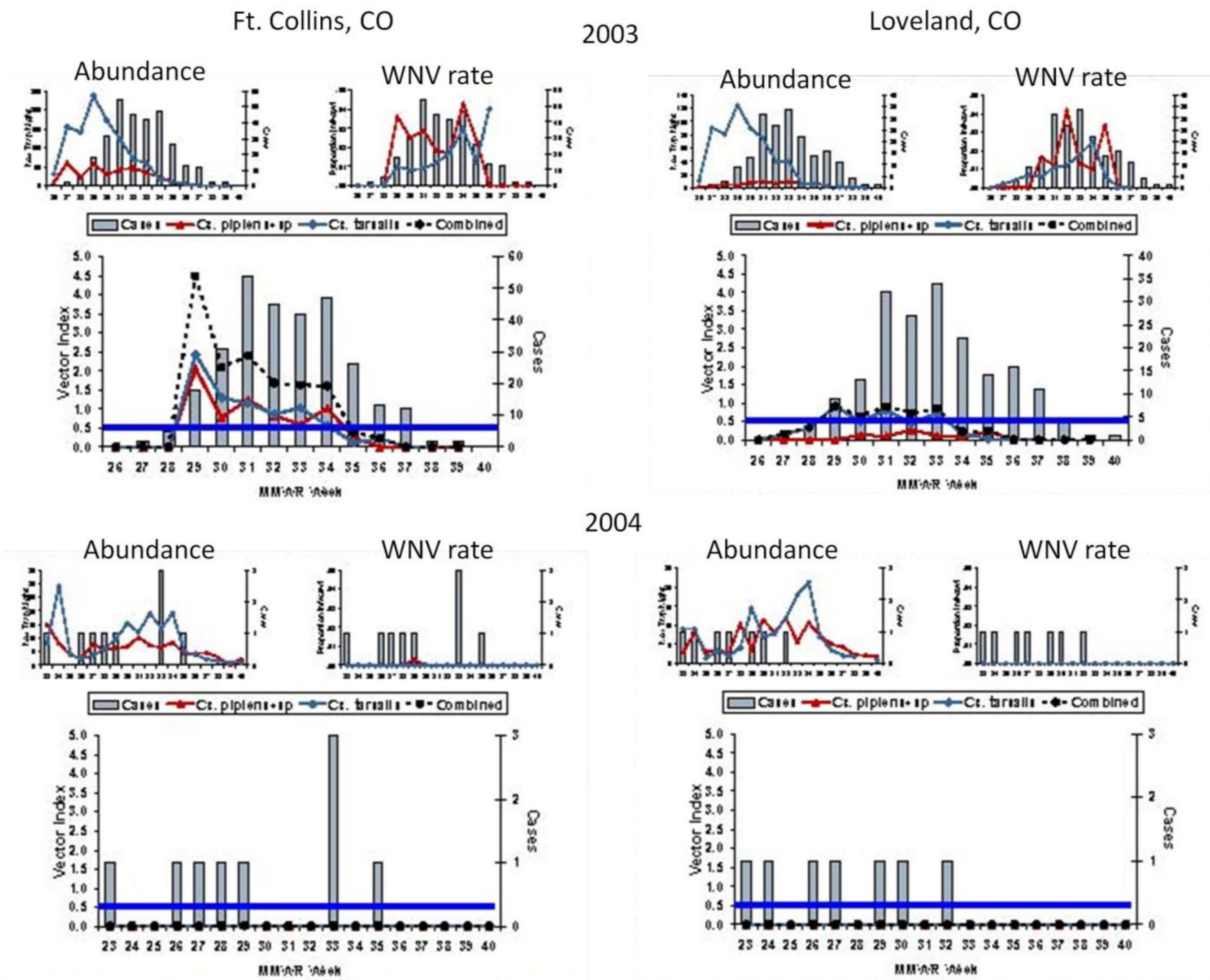
$$\mathrm{VI} = \sum_{i = species} NiPi$$

where *N* is the *mosquito abundance* (mosquitoes per trap night) and *P* is its MLE mosquito WNV infection rate, both for mosquito species *i*. If several species in a region are important bridge vectors infecting humans, the vector index is calculated separately for each species, and the estimates are summed over the various species *i* to yield the overall vector index.

The vector index estimates the number of WNV-infected mosquitoes per trap night. Its distribution is from zero to positive infinity. In low-level endemic circumstances it is commonly in the range of 0.1 to 0.3, and in large WNV epidemics it may range as high as 2 to 3.

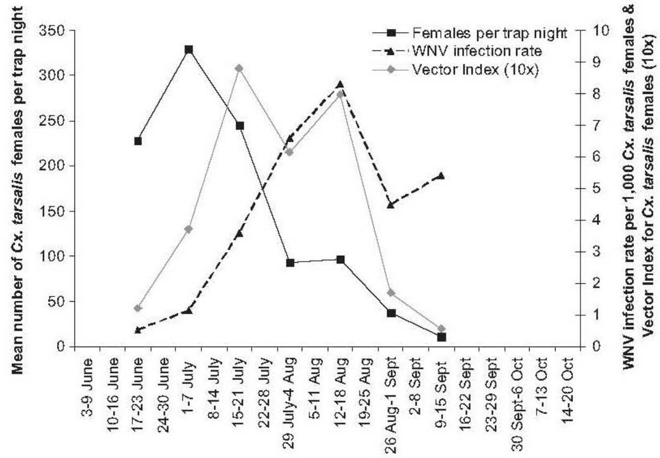
How Well Does the Vector Index Predict Human Epidemics?

Prior to the large epidemic of 2012, the predictive potential of the vector index had been tested in only two limited circumstances. In a poster presented at the 71st Annual Meeting of the American Mosquito Control Association in 2005 (available online[12]), Nasci et al. of CDC compared the association of the weekly vector index with the weekly incidence of human cases of WNND in two years (*figure below*). They concluded that in two Colorado cities a vector index value >0.5 predicted a WNV epidemic in 2003, and persistently <0.5 in 2004, no epidemic. Notice that in both cities the vector index first exceeded 0.5 in MMWR week 29 (mid-July), as in the Dallas study.

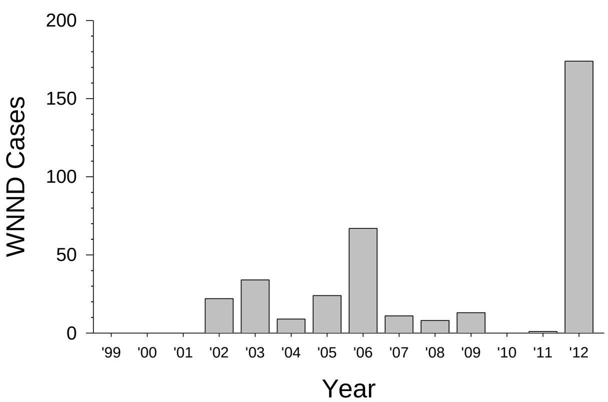


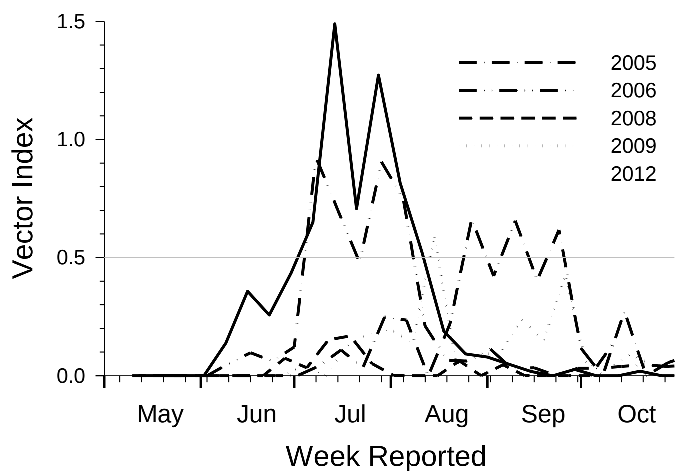
Bolling et al.[13] reported a WNV epidemic, also in northern Colorado, following 2 weeks after the vector index exceeded 0.5 (*figure to right*). The vector index then predicted the course of the epidemic, dropping below 0.5 only as the epidemic ended; whereas, the mosquito abundance (females per trap night) was not predictive.

These 2 studies, though suggestive, were not considered sufficient evidence for CDC to recommend routine use of the vector index as the basis for undertaking preemptive measures to prevent WNV epidemics.

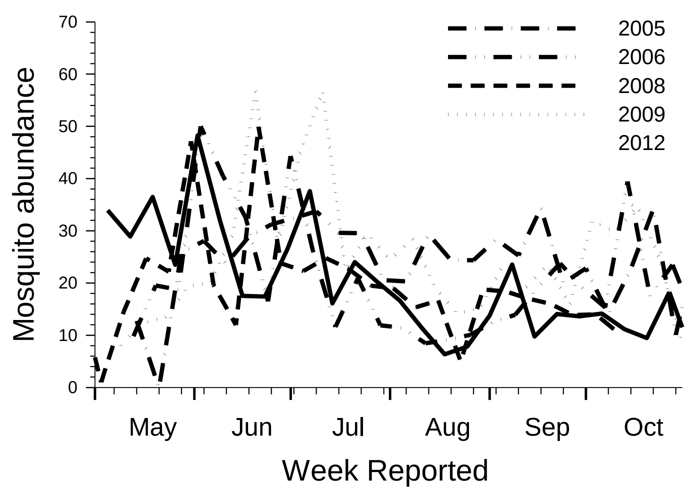


Following the large 2012 Dallas epidemic, Chung et al. performed a more thorough evaluation of the predictive value of the vector index.[2] In an 11-year archival database of prospective WNV mosquito and human case data, they reproduced the Nasci et al. finding, showing that a vector index value above 0.5 in June or July preceded the 2006 and 2012 WNV epidemics in Dallas County; whereas, in the remaining 9 years in which no WNV epidemics occurred, the vector index did not exceed 0.5 in June or July (2 *figures immediately below*).





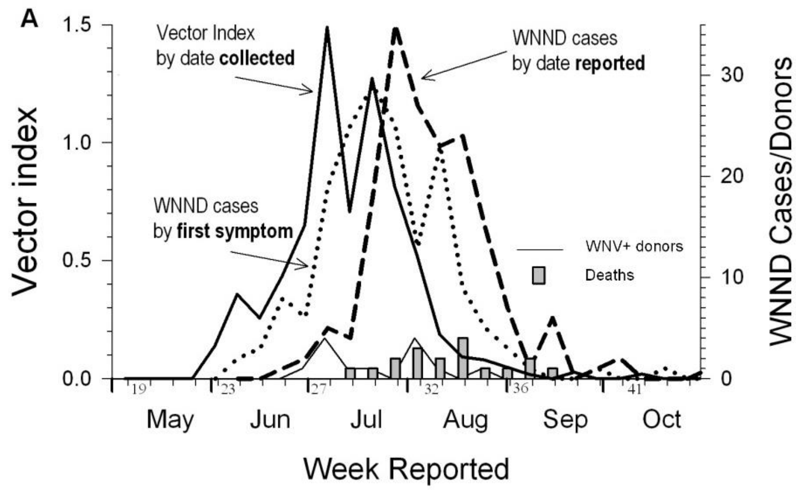
In years when the Dallas vector index first exceeded 0.5 in mid- or late-August (2005 and 2009 in *figure to right*), no human epidemic resulted. Possible explanations for "fizzling" of late season-appearing rises in the vector index are: 1) in late July mosquito abundance abruptly starts declining (Dallas data *in figure to the right*), reducing the risk of viral transmission to humans, 2) mosquito biting activity declines, and 3) the older infected mosquitoes either start dying or going into diapause ("hibernation").



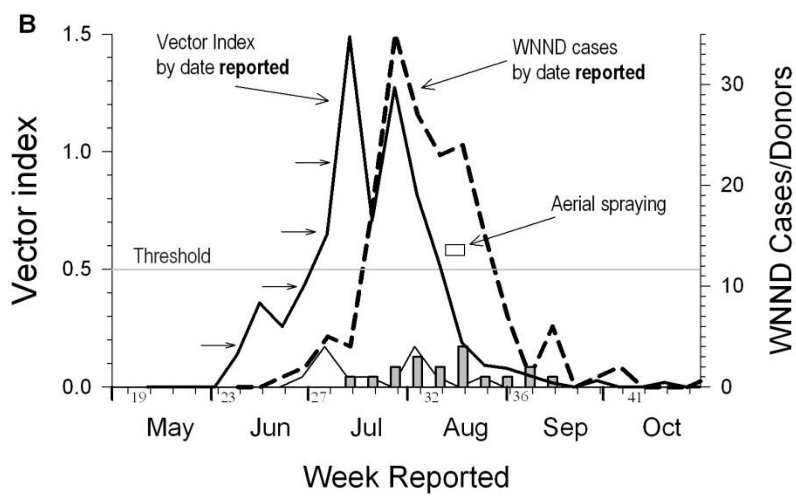
These findings support the Nasci et al.[12] and Bolling et al.[13] finding that the vector index predicts imminent WNV epidemics and that the critical threshold in Dallas is around 0.5. The Chung et al. finding further suggests that this threshold must be exceeded by mid-July for it to predict an epidemic. In retrospect the rise in the vector index to >0.5 occurred in mid-July in both the Nasci et al. and the Bolling et al. studies as well. Since this threshold may be influenced by many factors, however, the most predictive value should be determined empirically by analysis of historical data in every region.

A newly published study presenting the experience with predicting WNV activity over 5 years 2003-2007 in 15 Colorado counties found that the vector index accurately distinguished the two epidemic years from the low-activity years.[14] They used a higher scaled vector index calculation by summing the species-specific vector indexes for 4 mosquito species in contrast to the single species index used in prior studies. On their vector index, threshold values between 0.5 and 1.0 best distinguished epidemic from low human infection incidence 1-3 weeks later.

How Much Lead Time Does the Vector Index Provide?



In the 2012 Dallas epidemic, the increase in WNND cases by date of first symptom lagged about a week behind the increases in the vector index by date collected (*Fig. A to right*).[2] Since the average incubation period for cases is 7 days, the infecting mosquito bites appear to be increasing at the same time as the increases in the vector index. Consequently, most of the infecting mosquito bites for WNND cases in the Dallas epidemic occurred in June, July and early August. Since aerial spraying of insecticide was performed in mid-August, the vector index would probably have continued fluctuating through August in the absence of the intervention, as suggested by the results of the CDC 4-county evaluation (see below). The rise in the number of WNND cases by date reported to the health department occurred on average 2 weeks after the rise in cases by date of onset and 3 weeks after the rise in the vector index by collection date. Appropriate time-series analyses found these lag intervals between the curves to be statistically significant.[2]

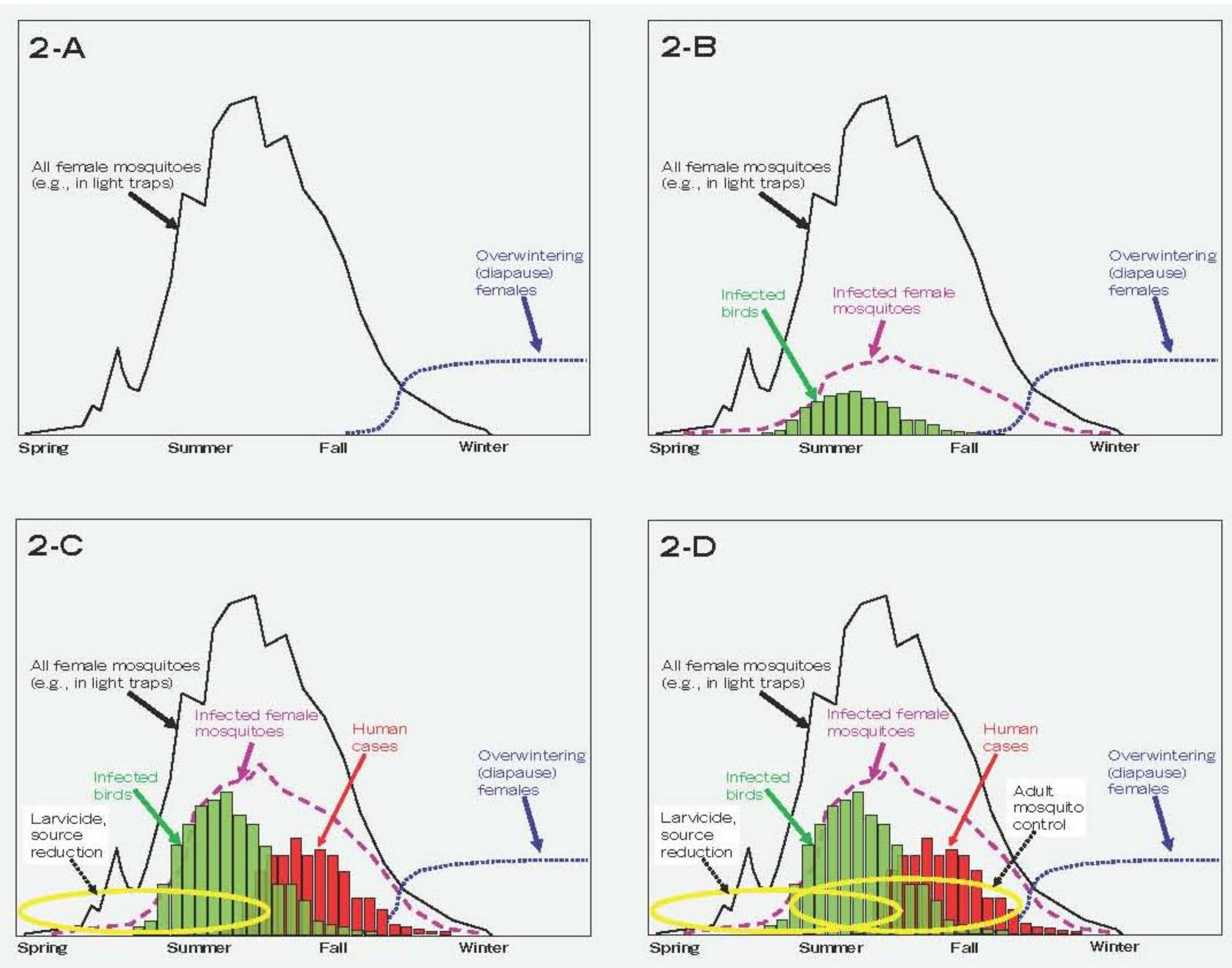


Moving the vector index curve to the right one week to allow for completion of mosquito testing and reporting and removing the curve of WNND by first symptom shows the information that would have been available to the health department for decision making, had this approach to surveillance been recommended at the time of the 2012 epidemic (*Fig. B to right*). With this information aerial spraying might have been undertaken as early as the end of the first week of July instead of mid-August, and 110 of the 173 WNND and 12 of the 21 deaths might have been prevented.

Methods for Preventing or Controlling Human WNV Epidemics

Epidemic Model for Basing Prevention Methods

A likely model for how human epidemics of WNV infection result is shown in the *figure below*.[15] (**Panel 2-A**) The virus is introduced into an environment of susceptible birds and mosquitoes either by overwintering in surviving infected female mosquitoes, their infected eggs, or migratory birds recently infected in Central or South America. (**Panel 2-B**) The earlier in the spring this occurs, as from an unusually warm, wet winter, and the lower the immunity level of the resident bird and mosquito populations, the earlier and larger the epizootic in the birds is likely to be. (**Panel 2-C**) The larger the epizootic becomes, the more it spills over into the human population. There are two strategies for reducing the mosquito population to prevent or control WNV epidemics: source reduction by **larviciding** or **adulticiding**.



Larviciding involves attempting to remove water sources in which the main bridge mosquito *Culex quinquefasciatus* breeds, such as bottle caps, French drains, overwatered lawns and birdbaths, as well as neglected swimming pools and abandoned tires. This is done both by educating the public to eliminate the water sources around their own houses and employing public health workers to remove sources in public areas and, with a new Texas state law, treating neglected swimming pools. Larviciding is used exclusively in the spring and early summer before viral amplification occurs to preempt an epidemic. **(Panel 2-D)** If preemptive measures do not prevent a human epidemic, larviciding and source reduction will no longer help, and the strategy must be shifted to adult mosquito control.

Adulticiding involves either **ground spraying** (spraying insecticide from trucks) or **aerial spraying** (from airplanes). Ground spraying may be used preemptively to target neighborhoods found to have positive mosquito surveillance traps or human cases, attempting to eradicate WNV epizootic foci before they become more intense, spreading the virus more widely through the bird and mosquito populations and then to humans.

Once a human epidemic begins, efforts to control it may involve either intensified ground spraying or aerial spraying. Aerial spraying has at least two advantages over ground spraying. First, aerial spraying can cover far larger areas more quickly and less accessible areas where trucks cannot go.[16,17] Second, aerial spraying delivers insecticide to the tops of trees where 80% of *Culex quinquefasciatus* are found. Aerial spraying achieves maximal mosquito control just after sunrise or just before sunset with 2-10-mph crosswinds.[17]

Aerial spraying to control arboviral infection epidemics in U.S. cities was first performed in Dallas to control the 1966 epidemic of St. Louis encephalitis.[5] Ever since 1966 Dallas County has annually renewed a contract with an aerial spraying company to spray over the county on short notice in case of a large arboviral epidemic, but has not had to exercise it again until 2012.

Ultra-Low Volume (ULV) Insecticide Spraying

ULV insecticide spraying, from either trucks or aircraft, uses special equipment that blows insecticide through a rotary atomizer that shears off extremely small droplets, from 1 to 150 microns in size. This allows the coverage of large areas with very small amounts of insecticide, and the size of the droplets can be varied since different species are maximally susceptible to droplets in different size ranges. Mosquitoes are maximally susceptible to droplets of 5-25 microns in size.[17] ULV techniques were developed in the 1950s to 1970s to control various agricultural pests from fungi to beetles and for control of arthropod-borne infectious diseases originally in developing countries, particularly trypanosomiasis carried by the tsetse fly in several African countries and Rift Valley fever carried by mosquitoes in Saudi Arabia.[16]

The protocol used for aerial spraying to control the 2012 Dallas WNV epidemic was for contract aircraft to pass over all affected areas twice 24 hours apart, using ULV spraying to deliver a product called *Duet Dual-Action®* containing two pyrethroid insecticides *Prallethrin* and *Sumithrin* along with a synergistic compound *piperonyl butoxide*. This combination of the two insecticides produces a phenomenon called “benign agitation” in which mosquitoes are agitated from a resting state to a non-biting flying state where they are more likely to contact a fatal dose of the pesticide. The piperonyl butoxide, developed in 1947, rapidly inhibits the mosquito’s cytochrome P450 that normally detoxifies pyrethroid insecticides and thus synergizes the insecticide effects. Piperonyl butoxide is used in a wide array of commercial insect control products for home and garden use. *Duet Dual-Action®* is approved by EPA as safe for use in controlling mosquito-borne epidemics in urban environments.

The ULV spraying protocol delivers approximately 15 mL (1 ounce) of the insecticide product per acre.

Literature Evidence that ULV Aerial Spraying Controls Epidemics

Numerous experimental studies have shown that two passes with ULV aerial spraying produces mosquito kill rates approaching 100% in open country, but since trees and shrubbery filter out 60-85% of the ULV droplets, the kill rates are lower for mosquitoes living underneath the tree canopy.[16,18] Kill rates for *Culex quinquefasciatus*, which lives predominantly in the tops of trees, is generally very good; whereas, that for *Culex tarsalis*, which is more prevalent in wooded terrain, is less.[18]

The best published evidence on the efficacy of aerial spraying for controlling urban epidemics of WNV in the U.S has come from studies done in Sacramento.[18,19] Looking first at the impact of aerial spraying pyrethrins/piperonyl butoxide from two Piper Aztec aircraft at 200 feet on 3 consecutive nights in August 2005, Elnaiem et al. measured a 75% reduction in mosquito abundance of *Culex pipiens* (the northern U.S. equivalent of *Culex quinquefasciatus*) compared with an equivalent unsprayed area (*see Table 1 below*).[18] As expected the reduction was only 49% with the forest-dwelling *Culex tarsalis*.

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Table 1. Effects of aerial spraying of pyrethrin insecticide on abundance of *Cx. pipiens* and *Cx. tarsalis* in north Sacramento, CA, during the week before and after spray in August 2005

Sampling area	Sampling period in relation to spraying	No. trap nights	Geometric mean no. (confidence intervals) of mosquitoes per trap night		
			Cx. pipiens	*Cx. tarsalis*	Total
Sprayed	Before	26	7.4 (5.2–10.2)	3.4 (1.8–5.9)	11.0 (7.4–16.1)
	After	20	3.7 (1.7–7.1)	1.1 (0.3–2.4)	4.6 (2.0–9.5)
Unsprayed	Before	26	2.0 (0.6–4.4)	4.8 (3.1–7.0)	8.1 (5.3–12.3)
	After	29	4.0 (1.8–7.8)	2.9 (1.3–5.7)	8.1 (4.2–14.9)
% control[a]			75.0	48.7	57.5

[a] The % control value was calculated using the formula described by Mulla *et al* (1971). Values in parentheses show 95% CI of the mean.

Moreover, the rate of WNV-infected mosquitoes decreased in the sprayed area, while increasing in the unsprayed control area (*Table 2 below*).[18]

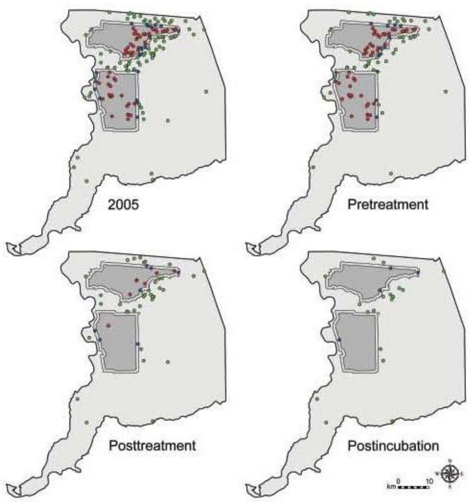
Table 2. Weekly infection rates of WNV in *Culex* mosquitoes collected from areas that were subjected to aerial spraying of pyrethrin insecticide and other unsprayed areas in Sacramento and Yolo counties, CA, July–August 2005[a]

Location	Sampling period	No. females	No. pools	No. +ve pools	% +ve pools	MLE[b] (95% CI)
North Sacramento spray area	Pretreatment					
	24–31 July	354	12	4	33.3	11.9 (4.2–28.3)
	1–7 Aug.	297	23	1	4.3	3.4 (0.2–16.9)
	Total	651	35	5	14.3	8.2 (3.1–18.0)
	Posttreatment					
	11–15 Aug.	145	19	0	0	0
	16–23 Aug.	85	11	1	—[c]	—*3
	Total	230	30	1	3.3	4.3 (0.3–20.3)
Unsprayed areas	Pretreatment					
	24–31 July	211	9	0	—[c]	—[c]
	1–7 Aug.	284	9	1	—[c]	—[c]
	Total	495	18	1	5.6	2.0 (0.1–9.7)
	Posttreatment					
	8–15 Aug.	346	21	4	19.0	12.1 (4.2–28.6)
	16–23 Aug.	251	28	1	3.6	3.9 (0.2–18.5)
	Total	597	49	5	10.2	8.7 (3.3–18.9)

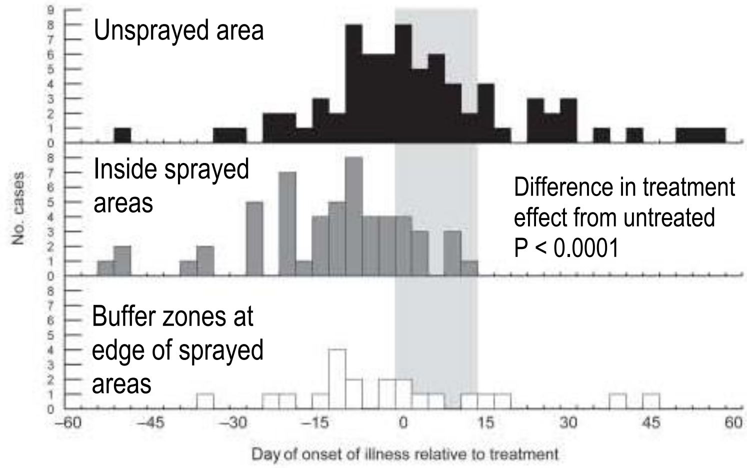
[a] Aerial spraying on 8–10 Aug. 2005.
[b] Bias-corrected maximum likelihood estimate of infection rate/1,000 mosquitoes (Biggerstaff 2006); 95% CI based on skewness-corrected statistic.
[c] No calculation of percentage of number of positive pools or estimation of infection rates were made, due to small number of individuals and pools examined.

The authors concluded that aerial spraying reduced the transmission intensity of WNV and thus the risk of human infection.

In the same 2005 WNV Sacramento epidemic, Carney et al.[19] compared the incidence of human WNV infections before and after the aerial spraying with incidence in unsprayed areas of the county adjacent to the sprayed areas (*2 figures top of next page*). The authors concluded that the aerial mosquito adulticiding was effective in ending the already established epidemic of human illness and death from WNV infection in the sprayed areas, while it continued on for over a month in the unsprayed and buffer areas.[19] Infection risks after spraying were 6-times higher in the unsprayed area than in sprayed areas, and spraying disrupted the WNV transmission cycle.

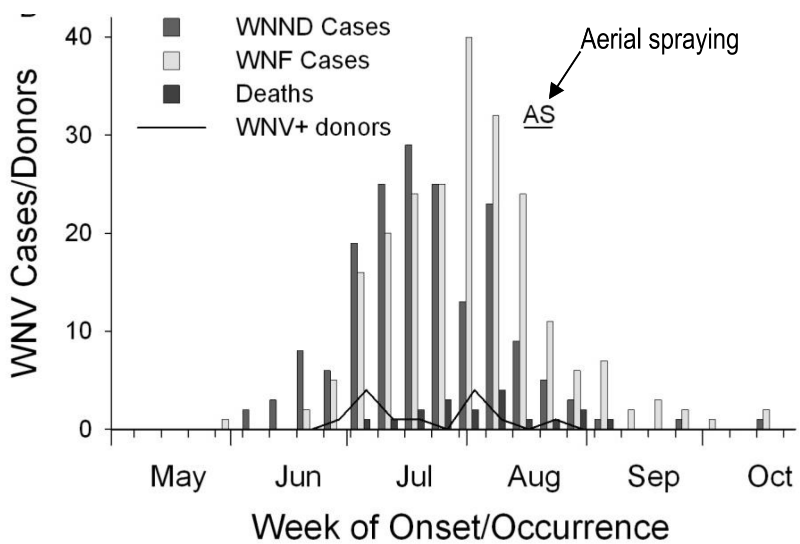


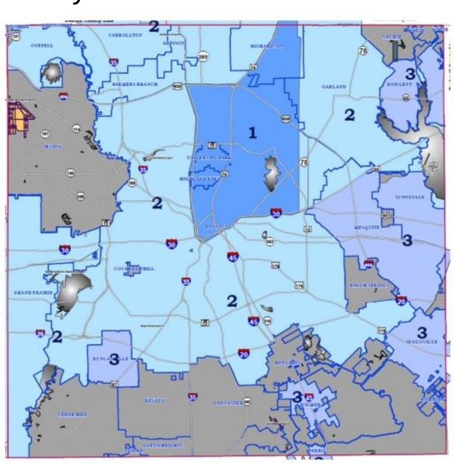
Shaded areas in Yolo Co. (Sacramento) were aerially sprayed in 2005. Dots are WNV cases.



Evidence that ULV Aerial Spraying of Insecticide Controlled the 2012 Dallas Epidemic

At the time of the 2012 epidemic the vector index had not been recommended, no threshold of the mosquito infection rate for initiation of aerial spraying had been established, and the county's WNV control plan included no provision for aerial spraying, even though the county had continued its contract for aerial spraying. As the incidence of WNND cases and deaths continued increasing in July, municipal and county health authorities intensified ground spraying, although insufficient numbers of trucks were available to cover the wide geographic distribution of positive mosquito traps and human cases. When the weekly incidence of human cases and deaths continued increasing through July in spite of intensified ground spraying (*figure above*), Dr. Luby and the infectious disease specialists advising the county health department recommended aerial spraying.



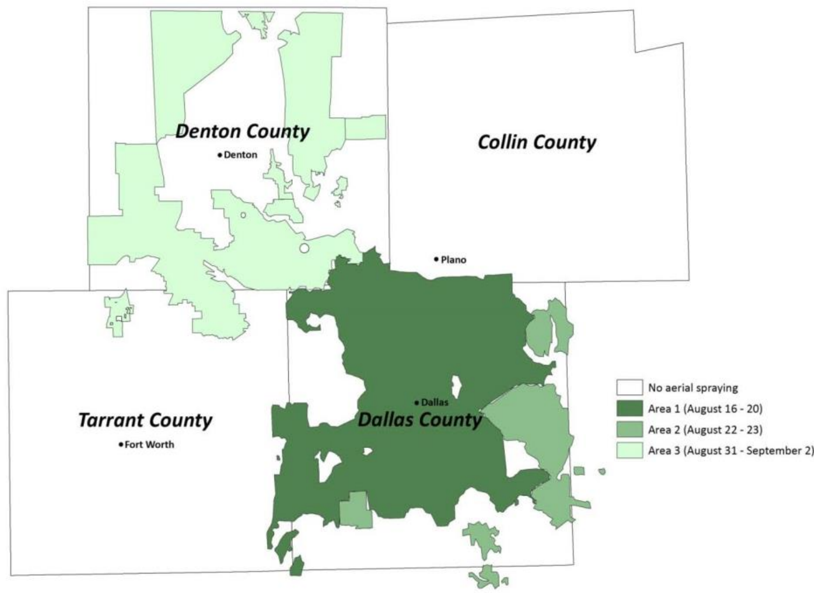


Aerial spraying was performed during the week of August 16-23 in 3 zones of Dallas County (*figure to left*).

This county map shows that 72% of the county acreage and 83% of its population were in the 3 aerial spray zones. Zones 2 and 3 were each sprayed on 2 consecutive nights as recommended for maximal effectiveness; whereas, zone 1, which included the heaviest concentration of WNND cases, was sprayed twice, but 4 nights apart, because of adverse weather conditions. The dark gray areas were not sprayed. Consequently, the spraying was not expected to be as effective in zone 1 as in zones 2 and 3.

With insufficient population density in the relatively small unsprayed areas, it was impossible to evaluate the impact of the aerial spraying entirely within Dallas County. After the epidemic ended, arboviral epidemiologists from the CDC's Vector-borne Diseases Division in Ft. Collins, CO, collaborated with the Texas Department State Health Services to perform the evaluation comparing sprayed and unsprayed areas in the 4 contiguous counties with high WNV incidence: Dallas, Tarrant, Denton and Collin. The areas sprayed and unsprayed are shown in Figure 2 (*to right*).[20]

Figure 2. Location of Area 1, Area 2, and Area 3 aerial spray events in northeastern Texas, 2012



Although the aerial spraying was undertaken late in the epidemic when the incidence was already declining in the unsprayed areas, the analysis found that the decline in WNND incidence rate in the sprayed areas significantly exceeded that in the unsprayed areas (*Table 3 below*). The CDC investigators concluded that the aerial spraying had ended the epidemic sooner than in the unsprayed areas.

Table 3. West Nile virus neuroinvasive disease cases, incidence rates per 100,000 population, and incidence rate ratios before and after aerial spraying in treated and untreated areas — Collin, Dallas, Denton, and Tarrant Counties, Texas, 2012

	Before aerial spraying			After aerial spraying						
Area	Cases	Population	IR	Cases	Population	IR	IRR*	(95% CI)	Ratio of IRRs†	(95% CI)
Treated	189	2,530,019	7.5	7	2,529,553	0.3	27.0	(12.7-57.4)	**2.55**	**(1.0-6.5)**
Untreated	148	3,085,121	4.8	14	3,084,758	0.5	10.6	(6.1-18.3)		

IR = incidence rates
IRR = Incidence rate ratio
CI = Confidence interval

*Incidence rate before aerial spraying/Incidence rate after aerial spraying
†IRR in treated areas/IRR in untreated areas

It therefore appears that the vector index gives advance warning of large WNV epidemics, and immediate aerial spraying at that point can curtail the epidemic and prevent the majority of cases and deaths.

The Politics of Preventing/Controlling WNV Epidemics

History of Political Opposition to Insecticide Spraying of Urban Populations

Mosquito abatement programs, like public health in general, has always been complicated by political conflict. This was well described in Tedesco et al.'s vivid account of the various political forces that shaped quite different approaches to mosquito abatement in the 4 mosquito abatement districts (MADs) in the Chicago area during the WNV epidemic of 2002.[21] The 4 MADs were governed by independent boards. The boards of 2 of the MADs adopted vigorous, timely mosquito abatement and public education policies. The North Shore MAD, located in a wealthy area with a highly educated population, mounted a limited response, primarily due to sustained opposition to insecticide spraying, expressed as angry demands to stop spraying at public board meetings, by residents concerned about adverse effects on human health and the environment. The South Cook County MAD implemented no control activities due to a combination of budgetary constraints and opposition to insecticide spraying by board leadership that believed adulticiding was ineffective in controlling WNV epidemics.

As a result some municipalities within the latter 2 MADs initiated spraying programs independently even though they were paying taxes to the MADs that were not acting. Some municipalities in MADs with vigorous adulticiding programs became concerned about the risk of WNV mosquito activity coming over from the neighboring South Cook MAD and sent their own insecticide trucks to spray in the neighboring MAD.

Late in 2002 as the gravity of the health effects of the epidemic penetrated the public consciousness, a larger public outcry demanding spraying caused board members to backtrack, but it was too late to change the course of the epidemic. Throughout, differences and changes in demand for spraying appeared closely related to public understanding of the disease and perceptions of the relative degree of risk from WNV infection and insecticide spraying. In succeeding years the leadership of the North Shore and South Cook MADs changed, and greater prevention efforts have emerged.

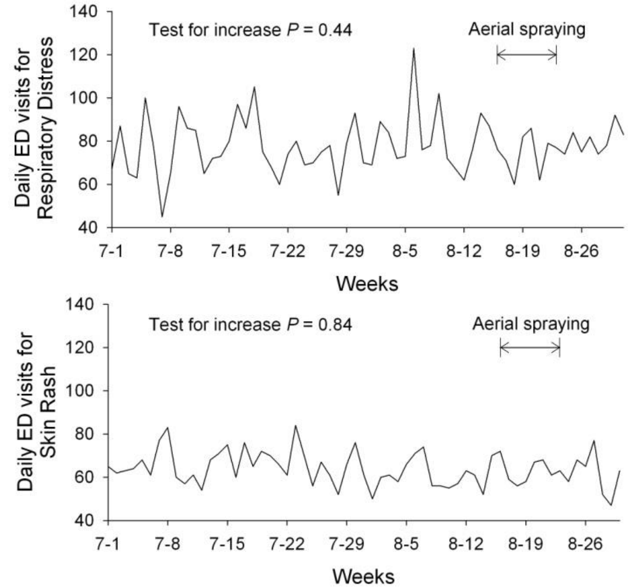
In the 2012 Dallas epidemic, when the Dallas County Medical Society leadership, mobilized by the infectious disease specialists, urged the health department to initiate aerial spraying to control the increasing number of WNND cases and deaths, vigorous opposition arose in the County Commissioners Court, supported by the impassioned testimony of a group of citizens opposed to any use of insecticides in disease control. Convinced of the need to begin aerial spraying but facing a likely negative vote in the County Commissioners Court, the County Judge, under his powers as head of the County's Emergency Response Authority, declared a public health emergency and unilaterally ordered immediate aerial spraying, which began a week later. The mayors of the various municipalities in the county endorsed the decision, which was generally well received by the general public in the most heavily affected communities. Political reverberations continued, however, and while most news reports have covered the aerial spraying positively, one journalist writing in the *Dallas Observer* has aggressively condemned it, positively reporting the arguments of the anti-insecticide activist group.

The Arguments Against Insecticide Spraying and Rejoinders

In January following the 2012 Dallas epidemic, members of the UT Southwestern faculty attended a meeting convened by the Dallas County Judge where the organizer of the anti-spraying Concerned Citizens group and her consultants presented their arguments supporting a permanent moratorium on all insecticide spraying in Dallas County. The most prominent arguments for the moratorium, with rejoinders, were as follows.

1. ***Concerned Citizens described telephone reports of large numbers of serious skin rashes and respiratory effects immediately following the aerial spraying that caused many to miss work and seek medical care***.

When the putative link between pesticide spraying in mosquito control and immediate illness has been examined epidemiologically, numerous scientific studies published in peer-reviewed journals have failed to find evidence leading to this conclusion (reviewed by Chung et al.[2]). Analysis of the trends in daily visits to emergency departments for acute illness by syndromic surveillance through the ESSENCE system covering the Dallas-Fort Worth Metroplex confirmed the published evidence by showing no increase in pulmonary or skin illness during or shortly after the aerial spraying[2] (*figure to right*).



2. ***A reputable Boston academic physician, asked to speak by Concerned Citizens, presented evidence from peer-reviewed research showing that low-level pesticide exposure of pregnant women sufficient to produce measurable urinary excretion of pesticide metabolites is strongly associated with lower IQ in their offspring***.

The summarized literature establishes a serious risk for fetal brain development from substantial, sustained pesticide exposure to the mother during pregnancy. All of the cited studies used the concentration of pesticide metabolites in urine as the measure of the mothers' pesticide exposure that they correlated with adverse effects on later intellectual development of the offspring. Those studies found that moderate and high urinary metabolite concentrations were associated with reduced IQ, but the lowest measurable urinary metabolite levels were not. Several published scientific studies measuring urinary pesticide metabolites after aerial spraying of pesticides to control mosquito-borne epidemics found no detectable increases in metabolite concentrations. This is because aerial spraying delivers less than 1 ounce of pesticide per acre of ground sprayed, the spraying typically occurs rarely and then on only two or three evenings, and the pesticides do not persist in the environment more than a day or so; whereas, the pregnant women studied in the cited papers were constantly exposed to much higher in-home environmental concentrations for the entire duration of their pregnancies, resulting in sustained, far higher levels of pesticide exposure. Thus, the cited studies are not relevant to assessing health effects of episodic ULV aerial spraying to control epidemics.

3. "The Sacramento Mosquito Control District, the most often quoted source of advice on WNV epidemic control, does not spray areas populated by humans."

The Sacramento aerial spraying program[19] estimated the number of people living in the areas covered by their 2005 aerial spraying program at over half a million. Moreover, in subsequent years their aerial spraying covered several million people, all without evidence of ill effects.

4. **"Aerial spraying does not control epidemics because the reduced mosquito population soon rebounds."**

   It is true that mosquito populations rebound within a couple of weeks after spraying has reduced their numbers. This does not mean, however, that aerial spraying is ineffective in controlling mosquito-borne epidemics. An epidemic of WNV infection is sustained by high levels of infection in birds that is spread and sustained by mosquitoes biting the birds. Birds infected with WNV remain ill with virus in their blood for approximately a week, at which time they either die or recover. To control an epidemic, the pesticide spraying need reduce the mosquito population for only a week or so, allowing time for the infected birds to become well and for virus to disappear from their bloodstreams before the mosquito population recovers. Just this transient drop in the mosquito population is generally sufficient to interrupt the transmission cycle and stop the epidemic.

5. **"Insecticide spraying is unnecessary because epidemics can be prevented or controlled by other measures not involving insecticide."**

   Entomologists with the Texas A&M Extension Service advise that, while larviciding measures may reduce mosquito abundance in localized areas, it has generally been impossible to change home-owner behavior sufficiently to affect mosquito abundance of *Culex quinquefasciatus*, the common house mosquito primarily responsible for urban epidemics in the south. Once a large WNV epidemic begins it is too late for larviciding intensification to affect its course, when only adulticiding has been shown to work.

6. **"Aerial spraying of pesticides causes the mosquito population to develop resistance to the pesticides."**

   While it is true that repetitive spraying of mosquito adulticides may eventually select for pesticide-resistant individuals, insecticide resistance has most commonly been recognized as a problem where area-wide pesticide spraying is done on a frequent basis, or where mosquitoes are repeatedly exposed to pyrethroid insecticides from other sources. A single, 3-day aerial spraying cycle, however, is unlikely to cause a long-term loss of susceptibility to the pyrethroid insecticides being used.

7. **"With better ground spraying from trucks, aerial spraying is unnecessary."**

   While ground spraying is thought to be effective in eradicating very localized "hot spots" of WNV mosquito infection, when large urban epidemics begin they often involve widespread mosquito infection that cannot be addressed by ground spraying in the short time required to stop a serious epidemic. In several of the large epidemics described in the literature, aerial spraying was undertaken after intensive ground spraying failed to control the problem.[19] Moreover, ground spraying exposes residents to 10 times the insecticide concentrations delivered by ULV aerial spraying.

8. **"Aerial spraying killed large numbers of bees and damaged the businesses of our beekeepers."**

   Careful studies of the effects of different droplet sizes of insecticide produced by ULV equipment shows that large flying insects are not affected by the droplet size that maximally kills mosquitoes.[17] Direct measurement of effects of aerial spraying on caged insects by entomologists at the University of California at Davis found that a standard aerial spraying protocol killed mosquitoes but had no significant effect compared with unsprayed controls on dragonflies, butterflies or bees.[22] In a survey of beekeepers in Sacramento all but one of 300 beekeepers surveyed reported no discernable effect of the aerial spraying on their bees. Studies of the effects of aerial spraying show small effects on some insects in exposed soil, but such ecological effects, like mosquito abundance, become undetectable after a few weeks (personal communication, Janet McAllister, CDC entomologist).

It was concluded that the arguments of Concerned Citizens were groundless and that the certain risk of crippling or fatal WNV infection outweighs the unsubstantiated risk of episodic ULV spraying with a very low concentration of agents approved by the EPA as safe for this purpose.

Editorial Comment: The Dilemma of Preventing WNV Epidemics

My provisional view from the evidence is that urban WNV epidemics will continue to occur and may become more severe as warming of our climate increases viral replication and mosquito biting activity. Large epidemics will continue to occur irregularly with low activity years in between, in a relatively unpredictable pattern.[1] I suspect the most aggressive efforts to preempt epidemics by urging the public to eliminate water sources around their homes, larviciding by health department workers, and ground spraying around positive mosquito traps and early WNND cases will not prevent the large epidemics, which appear geographically dispersed at the very start, possibly from introduction by highly infected migratory bird populations to highly susceptible local bird populations.

Evidence to date suggests that prospective mosquito trap surveillance by local health departments and rapid calculation of the *Culex quinquefasciatus* vector index with a threshold of 0.5 in June or July gives early warning of an impending large epidemic in time to prevent most of the cases if aerial spraying is initiated immediately.

The dilemma results, however, when the political decision-makers are suddenly faced with the decision to order aerial spraying during the early incubation period before the numbers of WNND cases and deaths begin mounting, knowing the ambivalence of the public and the reluctance of political leaders, driven by protests of small numbers of vocal anti-pesticide activists.

As a result, when the next large epidemic arrives, I predict there will be strong inertia to postpone aerial spraying until media reports of growing human illness and death rally enough public support to outweigh the protesters and political opposition. By then, however, the infecting mosquito bites for most of the eventual WNND cases and deaths will already have occurred and it will be too late for intervention to have a large effect.

On the optimistic side, the experience of the 2012 nationwide WNND epidemic stimulated CDC to publish a new guideline for the first time formally recommending use of the vector index and a threshold for action.[6] Whether the new guideline coupled with education of the public and elected leaders will work remains to be seen.

A potentially useful proposal is the establishment of a Mosquito Abatement District (MAD) in Dallas County or a wider area. This would move the decision-making authority from elected officials to an appointed MAD board. If appropriately appointed and funded, this might solve some of the lingering problems of standardizing the mosquito trap surveillance, ensuring more timely testing of mosquitoes and calculation of the vector index, and streamlining decision-making on insecticide spraying. Presenting the experience of regions with MADs, such as Sacramento, Houston and Chicago, might someday be useful to interest Dallas-area elected officials in the idea.

Finally, the prospect of increasing severity of WNV epidemics and this dilemma in timely intervention suggest the need for an effective vaccine to protect the susceptible segment of the population. Several human vaccines are in development or testing, and potential differences in host immunity that might identify the susceptibles for selective immunization are in progress.

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