The Massachusetts Department of Public Health

Report of Eastern Equine Encephalitis Expert Panel

June 2012

Introduction

Eastern equine encephalitis (EEE) is a serious viral disease of people with 30-50% mortality and lifelong neurological disability among many survivors. Historically, in Massachusetts, clusters of human cases have occurred over a period of 2-3 years, with a variable number of years between clusters. In the years between these case clusters or outbreaks, isolated cases can and do occur. Outbreaks of human EEE disease in Massachusetts occurred in 1938-39, 1955-56, 1972-74, 1982-84, 1990-92, and, 2004-06. Two cases of EEE occurred in both 2010 and 2011; one of the cases in each of these years occurred in visitors to Massachusetts.

While the overall number of cases remains small when compared to many other infectious diseases and other causes of death or disability, the impact at the individual, family, and community levels is significant, and this disease warrants significant public health attention. There are multiple agencies and organizations within Massachusetts that cooperate to address EEE surveillance and response concerns and activities, and there is a significant amount of local expertise and experience. However, in response to indications that risk from EEE may be increasing, and a sincere desire to better understand the impact of any changing ecology and improve risk mitigation efforts, the Massachusetts Department of Public Health convened a panel of external authorities and experts to review and comment on the current EEE surveillance and response program.

Expert Panel

Experts in the fields of mosquito biology, toxicology, ecology, climate change, public health and infectious disease were invited to participate. With one exception, the panelists were chosen specifically because they were not already involved in the Massachusetts arbovirus surveillance and mosquito control processes, and could be expected to provide fresh perspectives. A local health agent from southeastern Massachusetts was included to monitor the process and provide local context.

- John-Paul Mutebi, PhD: Entomologist, Centers for Disease Control and Prevention, Division of Vector-borne Diseases
- Nicholas Komar, SD: Biologist, Centers for Disease Control and Prevention, Division of Vector-borne Diseases
- Cathleen Drinan, M.Ed.Health Promotion: Health agent, Town of Halifax, MA
- Richard Primack, PhD: Conservation biologist and plant ecologist, Boston University
- Barbara Beck, PhD: Toxicology and human health risk assessment consultant, Gradient, Cambridge, MA
- Alan Dupuis, BS: Zoonotic disease research scientist, Arbovirus Laboratories, Wadsworth Center, New York State Department of Health
- Laura Kramer, PhD: Zoonotic disease research scientist, Arbovirus Laboratories, Wadsworth Center, New York State Department of Health
- Marm Kilpatrick, PhD: Disease Ecologist, University of California, Santa Cruz
- John Howard, DrPH: Research scientist, Arthropod-Borne Disease Program, New York State Department of Health (retired)
- James McGuire, MD: Infectious disease physician, Brigham and Women’s Hospital, Boston, MA

The EEE Expert Panel review process began with a webinar on February 3, 2012 to provide an orientation on EEE in Massachusetts and the current surveillance and response system. Conference calls were held on February 21, March 8 and 23rd, and April 13. One call included three health agent representatives serving southeastern Massachusetts cities and towns. The webinar and conference calls were recorded and audio versions were made available for participants to review. The panel's work was completed during an in-person meeting on April 23, 2012 from 9-4 PM, hosted by the Massachusetts Commissioner of Public Health, John Auerbach.

Initially, the panel was asked to discuss and provide feedback on a specific set of concerns and questions, although discussions were not limited to these topics. These questions were:

1. Is there evidence that the historical EEE cycle in Massachusetts has changed; i.e. has there been an increase in the frequency of human cases?
2. If yes, is it attributable to anything specific, such as climate change?
3. Are there indicators of human risk that we are not utilizing or are under-appreciating?
4. Is there evidence to support the use of some type of pre-emptive aerial mosquito control activity, either larviciding or adulticiding?
5. What indicators should be used to trigger an aerial adulticide intervention?

During the panel's considerations, MDPH shared historical surveillance data, performed additional data analyses on request and reviewed analyses conducted by panelists. A moderated discussion format was used to achieve consensus on panel opinions and recommendations. This report summarizes the conclusions reached during these discussions, and also indicates those points where complete consensus was not achieved.

Frequency of Human Cases

The number of human cases that occurs during a given outbreak year(s) has decreased substantially since the first two outbreaks of disease occurred in 1938 and 1955 (Figure 1). However, the average time between outbreak years with multiple cases has also decreased (Figure 2). The panel concurred that, over time, the probability that a human EEE case would occur in any single year has increased.

The ability to rigorously evaluate whether or not there has been a change in the geographic distribution of disease based only on the location of human cases is limited. In the first few outbreaks, cases were more likely to be residents of Suffolk, Middlesex and Norfolk counties. After 1990, cases are more likely to be Plymouth, and to a lesser extent, Bristol County residents (Figure 3). Because cases are recorded based on county of residence and not exposure location, it is not clear if this is due to human factors, i.e. Suffolk County residents being exposed to EEE virus at their summer residences in southeastern Massachusetts during the middle part of the 20th century, or if it represents a true change in the distribution of the EEE virus. However, information from the 1938 outbreak (Feemster, 1938) reveals that while equine cases occurred in Suffolk, Middlesex and even Worcester and Essex counties, the majority of them were distributed throughout Norfolk, Bristol and northern Plymouth counties indicating that southeastern Massachusetts is an area of both current and historic risk.

Identification of EEE virus in mosquitoes, animals or humans has occurred sporadically in other parts of Massachusetts. However, only the northern portion of Essex County, which borders New Hampshire, has shown a period of sustained virus activity. Risk in this area may not correlate with risk in southeastern Massachusetts.

An in-depth analysis assessing the relative population abundances of all species of mosquitoes by geographic area was strongly recommended by the panel for analyzing virus distribution trends.

Causes of Change

On the basis of genetic analyses of EEE virus isolates from Massachusetts performed by MDPH and presented to the panel, there was agreement that the observed, underlying pattern of the virus cycle has not changed over time; genogroups of the virus are periodically introduced into Massachusetts, persist for several years and then disappear (Figures 4 and 5). Human cases do not always occur every year a particular genogroup is identified in mosquitoes; however, based on the data from 1970-2011, identification of a new genogroup often occurs in conjunction with human cases the same year. Currently, no evidence exists that there has been a change in the virulence or pathogenicity of the virus, but neither is there sufficient evidence to completely rule this out. Genetic analysis should continue going forward to monitor for the emergence of new genogroups and to observe their relationship with the incidence of human disease. Changes in virus pathogenicity can and should be investigated simultaneously; this may be most effectively done through collaborations with academic institutions or the Centers for Disease Control and Prevention.

There was consensus that several elements of the ecologic cycle have not been completely elucidated. These uncertainties include:

- source(s) and timing of introduction of new virus genotypes to Massachusetts;
- mechanisms of virus persistence from year-to-year also termed “overwintering”;
- the extinction processes that result in elimination of a particular viral genogroup; and
- the relative importance of *C. melanura* (higher infection rate, but low preference for feeding on mammals) versus “mammal-biters”, such as *Coquellitidia perturbans* (low preference for birds, but high numbers and preference for mammals) as vectors of EEE to humans and other mammals.

Aspects of the ecology of EEE that are more certain and were agreed upon by panel members include:

- identification of *Culiseta melanura,* a largely bird-biting mosquito whose preferred breeding and feeding habitats are white cedar and red maple swamps, as the principle vector of EEE virus, responsible for amplification of the virus during the summer;
- songbirds of various species that live in and around white cedar and red maple swamps serve as reservoirs and amplifying hosts of the virus; and

Susceptible species such as horses, camelids, and humans do not play a role in the virus amplification cycle and are considered to be dead-end hosts to the virus.

No clear evidence supporting any single explanation for the observed changes in the frequency of occurrence of human cases emerged from the panel discussions. Factors that were considered likely to play a contributory role include:

- evolutions of land use patterns including changes in human population densities adjacent to both cedar swamp and cattail marsh mosquito habitats;
- evolution of land use patterns;
- alterations in the relative population abundance of particular species of songbirds, especially the American robin, and changes in bird migration patterns and seasonal timing;
- changes in average temperatures and precipitation events related to climate change.
- changes in mosquito abundance, community composition, feeding patterns, or movement behavior.

Data exists to further investigate some of these factors and the panel recommended that these analyses be pursued.

MDPH surveillance data show evidence of small increases in both *C. melanura* and *Cq. perturbans* mosquito populations over the last 8 years. The importance of this observation over such a short time span is unknown but the panel has suggested analysis of earlier data to further evaluate this trend and close observation of the populations moving forward. The in-depth analysis recommended previously, looking at the relative population abundances of all species of mosquitoes by geographic area, was strongly recommended as a means of analyzing mosquito population trends in conjunction with trends in virus distribution.

Human Risk Indicators

In 2011, EEE virus infection was not identified in a mammal prior to the first human infection. Although identification of viral spillover into a mammal is indicative of elevated human risk from EEE, the panel agreed that lack of an animal case should not preclude an assessment of elevated human risk when other indicators are present.

The panel affirmed that MDPH mosquito surveillance does provide an effective way to compare abundance of and infection rates in *C. melanura* from week to week, year to year, and place to place. However, these data are limited by variable weather during trap nights, diminishing MDPH field staffing resources, and incomplete information on mosquito control activities conducted adjacent to traps; the latter two are modifiable factors that the panel recommended addressing if possible. In addition, neither mosquito abundance, measured as number of mosquitoes per trap per night, nor numbers of infected mosquito pools (grouped samples of up to 50 mosquitoes) nor infection rates, measured as the minimum number of infected mosquitoes per 1000, correlate closely enough with the occurrence of human cases (Figures 6,7 and 8). Multiplying mosquito abundance by the infection rate creates a new risk indicator called the Abundance Infection Factor, AIF, which provides a measure of the density of the infected mosquito population. This type of approach has been used for assessing West Nile virus risk and has been referred to in the literature as a vector index (Gujaral *et al.*, 2007) or a risk index (Kilpatrick *et al.*, 2005). Initial analysis with data from the last eight years indicates that an AIF of greater than 40 correlated better with the occurrence of human cases than either of the factors

on their own (Figure 9). An AIF over 40 aligns with human EEE cases in all but one recent year. The panel supported using AIF as the primary risk assessment measure and recommended additional analysis to assess the utility of the AIF with the earlier historical data. Going forward, the AIF will be employed to better define its use as a tool for predicting human risk.

Other historical indicators of risk that the panel agreed should continue to be evaluated include:

- above average rainfall in the prior fall and spring,
- mild winters with insulating snow cover,
- EEE activity in the previous year,
- any EEE virus isolations from mosquitoes prior to July 1,
- isolation of EEE virus from a mammal-biting species of mosquito,
- infection of a human prior to mid-August, and
- higher than average summer temperatures which accelerate the mosquito reproductive and development cycle and shorten the time interval between a mosquito becoming infected with EEE virus and when it becomes capable of transmitting the virus.

Two additional suggestions were to: consider the use of dead bird testing outside of traditional areas of EEE activity to evaluate changes in the geographic distribution of the virus; and to consider testing mosquito samples for Highlands J virus, as presence of this virus may correlate with appearance of EEE virus. These recommendations did not achieve complete consensus from the panelists and recent data from New York did not support the utility of Highlands J virus as a consistent predictor of EEE risk.

Evidence Regarding Pre-emptive Larviciding or Adulticiding Mosquito Control

The panel agreed on the following points related to larviciding for control of EEE virus. Larviciding to kill juvenile *C. melanura* mosquito stages where they live in water-filled crypts under tree roots in white cedar and red maple swamps is difficult. Bti, *Bacillus thuringiensis* var israelensis, a bacteria used as a biological control for many species of mosquito larvae and which is widely employed in Massachusetts for larviciding against nuisance mosquito species and those that carry West Nile virus, does not penetrate into crypts and is not persistent enough to diffuse into them over time. Methoprene, a chemical also used as a larvicide, when applied as a granule or pellet, will penetrate the tree canopy of the swamps and is persistent enough to diffuse into crypts. However, methoprene's potential for negative impacts on non-target aquatic makes it undesirable for use in sensitive ecologic areas and it is unlikely to be approved for this use in environmentally sensitive areas in Massachusetts.

C. melanura remain dormant through the winter (overwinter) as larvae in crypts in the cedar swamps. The first generation begins to emerge as adults in late April and that population peaks by early June. These adults feed on the birds roosting in and around the swamp and lay the next generation of eggs in the crypts. EEE virus is not detected in this generation of mosquitoes, but they are important because the population of this generation of mosquitoes will largely determine the abundance of second-generation adult mosquitoes later in the season. As the second generation of adults emerge in July and August, EEE virus can be isolated from both mosquitoes and birds and the amount of virus present increases and remains elevated through August. Both mosquito numbers and virus present in the birds and mosquitoes begin to decrease by September,

although the actual infection rates in older mosquitoes during fall may remain high (Figure 10). A logical mosquito control intervention point would seem to be to apply an adulticide before the peak of the first generation of mosquitoes to prevent egg-laying and reduce the second generation's population. For maximum effectiveness this intervention would occur during the middle of May. However, average night-time temperatures in Massachusetts at that time of year are below the 60-64 ºF threshold recommended for the effective application of a mosquito adulticide. Application of pyrethroid-based adulticides is effective only when the spray comes into direct contact with actively flying mosquitoes and it has no residual effect. The panel concluded that pre-emptive adulticide mosquito control applications are not considered practical or worthwhile for reducing human risk from EEE in Massachusetts.

Human and Ecological Health Effects of Sumethrin and Piperonyl butoxide (PBO)

During the discussion of mosquito control techniques, a concern was raised about the human and ecological health effects of the mosquito adulticide, Anvil®, used in Massachusetts. The United States Environmental Protection Agency's Reregistration Decisions (REDs) for sumethrin and piperonyl butoxide (PBO), the active ingredients in Anvil®, were reviewed. Two application studies (Peterson *et al*. 2006; Macedo *et al*. 2010) that assessed actual deposition of the ingredients following aerial and truck-based applications provided additional information. The studies evaluated potential human health risks, considering multiple pathways, such as inhalation and inadvertant soil ingestion from aerial deposition on soil. Human health risks were calculated using "conservative" exposure assumptions and toxicity criteria, *i.e.* assumptions that tend to overestimate risk. Moreover, the application rate in these analyses was greater than that proposed to be used for aerial spraying in Massachusetts. When applied in a manner consistent with its' labeling, the panel agreed that the evidence indicates that human exposure to both active ingredients falls below levels of concern for all age groups and exposure routes.

Studies do indicate that there are effects on non-target insects associated with these ingredients. The panel agreed that widespread adulticiding for disease risk mitigation should be limited to public health emergencies. Pesticide application should be done after sunset using ultra-low volume applicators to be most effective against the primary vector of EEE virus, *Culiseta melanura*, and to minimize non-target effects.

Triggers for an Aerial Adulticide Intervention

The panel was unanimous in its opinion that it was not possible to prevent every case of human illness caused by EEE virus. There was also unanimity that aerial applications of mosquito adulticide can be one effective tool employed to reduce, but not eliminate, risk of human EEE virus infections, but that aerial spray interventions should not be used in the absence of human risk indicators. There was also agreement that personal prevention practices such as repellant use, decreased outdoor activity during peak mosquito hours, and clothing to reduce skin exposure are effective and should form the basis of all risk reduction efforts.

The panel was not able to recommend precise triggers for determining the need for an aerial application of adulticide, in part because of the imperfect nature of indicators of human risk and because there were areas identified as needing further evaluation. There was support from the

panel for the components of the Massachusetts Arbovirus Surveillance and Response Plan as it is currently structured; there was also strong support for the suggestion that due to the inability to precisely predict risk, that the threshold at which an aerial adulticide intervention is considered should be lowered and that aerial spraying of focal areas determined by risk data should be considered. There was also strong concern that conducting an aerial adulticide intervention would lead to a false sense of security among members of the public, leading to a reduction in personal prevention practices. The panel urged that communication messages be structured accordingly.

Summary

There should be a general expectation that there will be some risk from EEE virus every year. Risk assessments using a combination of historical indicators and newer data analysis techniques as endorsed by the panel should be performed. Consideration of the need for aerial adulticiding intervention, perhaps in focal areas, should occur before risk levels become critical but should not be considered in the absence of indicators of human risk. Personal prevention practices are essential for risk reduction and should be incorporated into all risk communication messaging.

Addendum

Since October 2011, in addition to the EEE Expert Panel, the Massachusetts Department of Public Health has consulted with multiple local health departments, participated in several community forums with local officials and responded to requests for information from elected officials from southeastern Massachusetts. These discussions have resulted in the following recommendations to improve the EEE surveillance and response process.

1. MDPH will seek to improve communications with local health agents through at least biweekly conference calls during risk season and through targeted HHAN messages with local risk updates.
2. MDPH will issue specific recommendations for curtailment of outdoor activities near dusk for common adoption by affected cities/towns.
3. MDPH will work with the SRMCB and the MCPs to investigate opportunities to increase the frequency of mosquito collections and enhance the timeliness of mosquito collection testing by the State Laboratory Institute.
4. MDPH will explore the utility of new surveillance analyses (3D time/risk mapping; Abundance Infection Factor) to current surveillance-based calculations of human risk, during 2012.
5. MDPH will work with agency partners to review rules governing ground spraying to more explicitly permit off-road access.
6. MDPH will lower the threshold for consideration of aerial spraying to mitigate risk of human illness in the 2012 Massachusetts Arbovirus Surveillance and Response Plan and modify the factors used to define the two highest human risk categories.
7. MDPH will work with the SRMCB and MCPs to consider options for focal area aerial spraying as an alternative to full regional spraying and to explore potential local assets/airplane-based equipment to support more rapid and focused spray actions.

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Figures

Figure 1. Number of human EEE cases each year from 1938 to 2011.

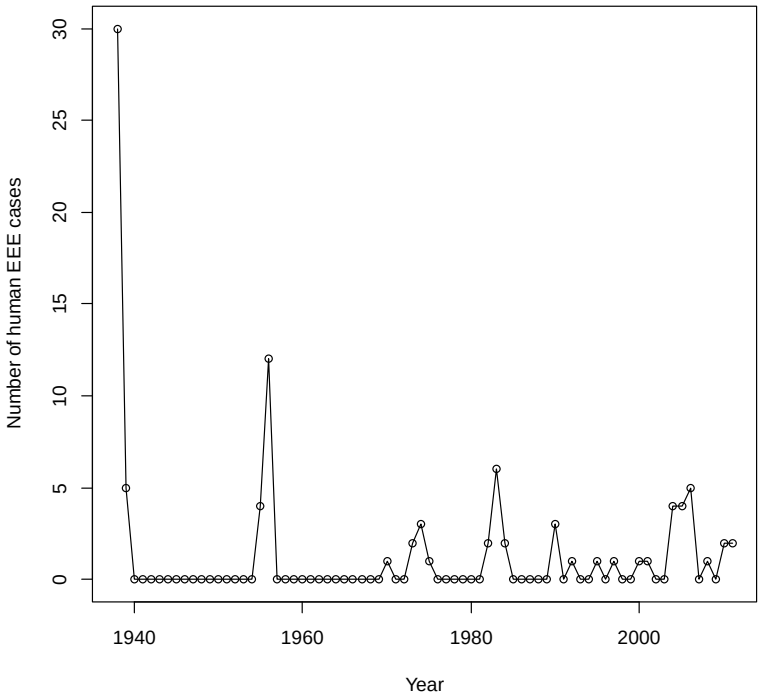


Figure 2. Intervals (in years) between years with any human EEE cases. (Position of circle on x-axis is the midpoint between years with cases).

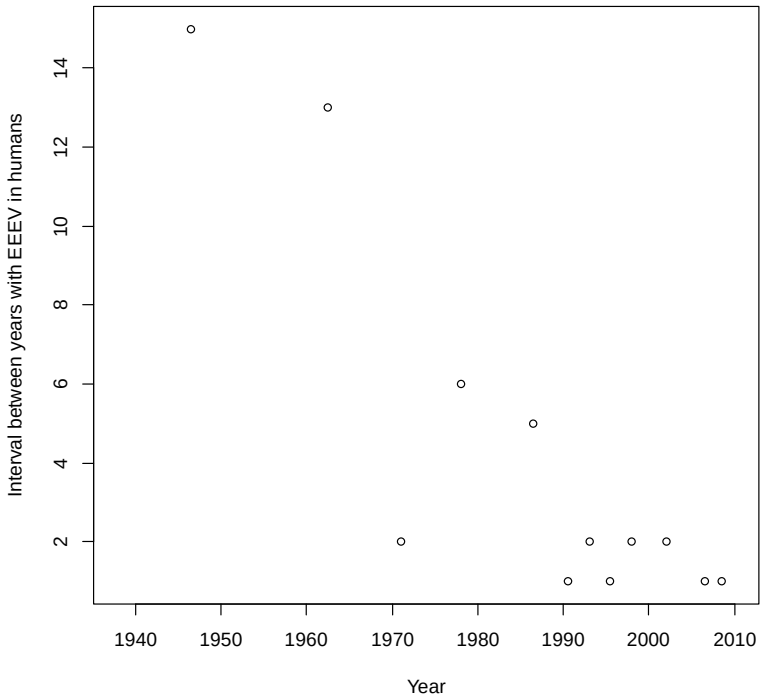


Figure 3. Percentage of cases by county of residence and year(s)

Year	Bristol	Middlesex	Norfolk	Plymouth	Suffolk
1938-39	8%	28%	24%	32%	8%
1955-56	0%	6%	44%	38%	13%
1970	0%	0%	0%	100%	0%
1973-75	0%	20%	60%	20%	0%
1982-84	0%	33%	44%	22%	0%
1990	0%	0%	0%	100%	0%
1992	0%	0%	100%	0%	0%
1997	0%	0%	100%	0%	0%
2000	0%	0%	0%	100%	0%
2004-06	14%	7%	14%	64%	0%
2010-11	50%	0%	0%	50%	0%

Figure 4. EEE virus genotypes and number of isolates by year.

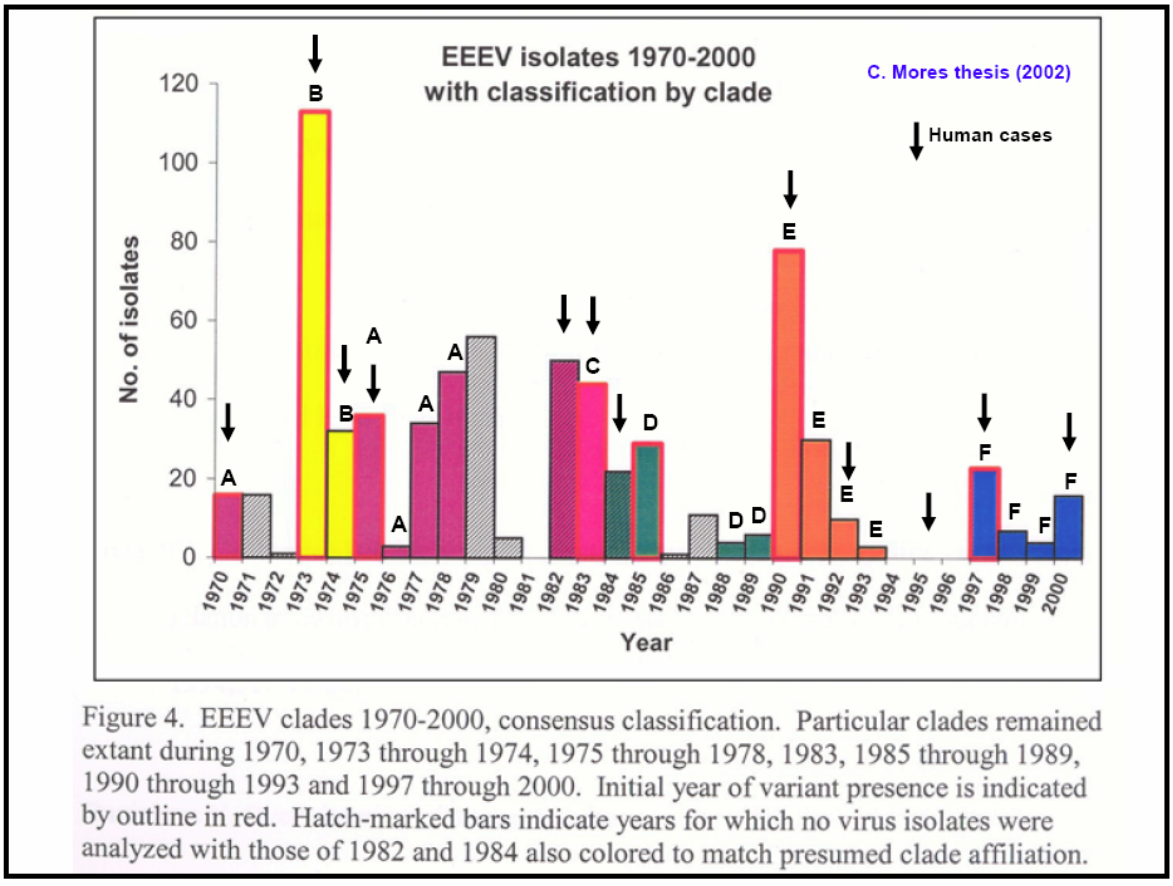


Figure 4. EEEV clades 1970-2000, consensus classification. Particular clades remained extant during 1970, 1973 through 1974, 1975 through 1978, 1983, 1985 through 1989, 1990 through 1993 and 1997 through 2000. Initial year of variant presence is indicated by outline in red. Hatch-marked bars indicate years for which no virus isolates were analyzed with those of 1982 and 1984 also colored to match presumed clade affiliation.

Figure 5. EEE virus genotypes of human cases, 1968-2011.

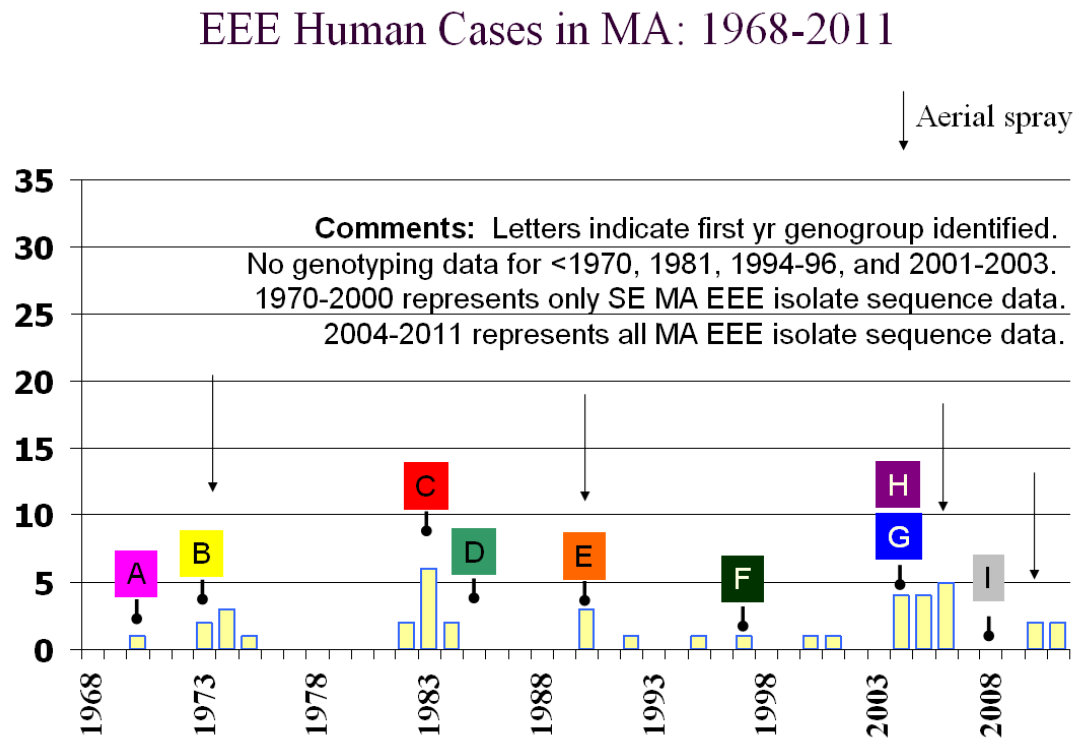


Figure 6. Annual *C. melanura* minimum infection rates (MIR) from long-term trap sites and human EEE cases, 2004-2011

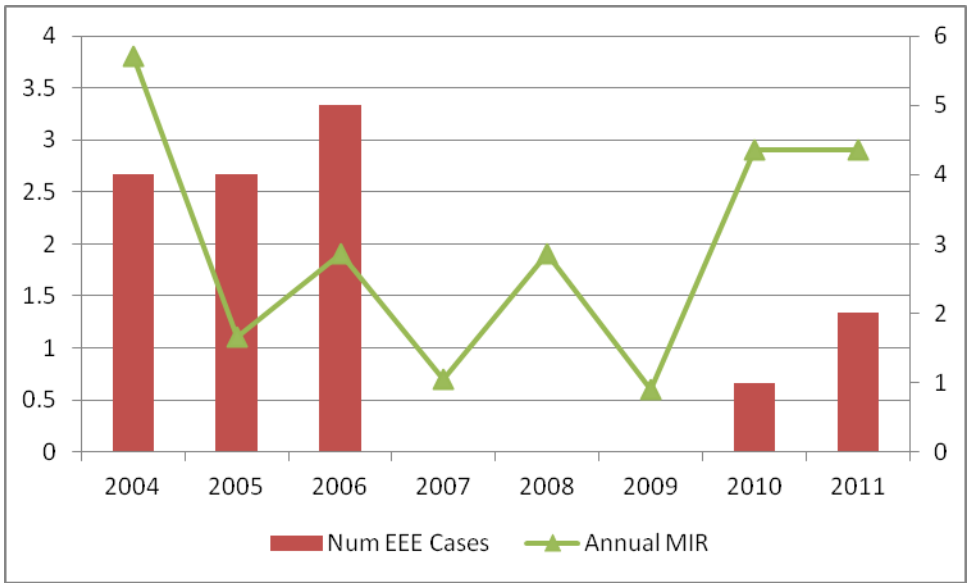


Figure 7. Number of EEE virus positive mosquito samples (i.e. pools) and number of human cases, 1970-September 9, 2011

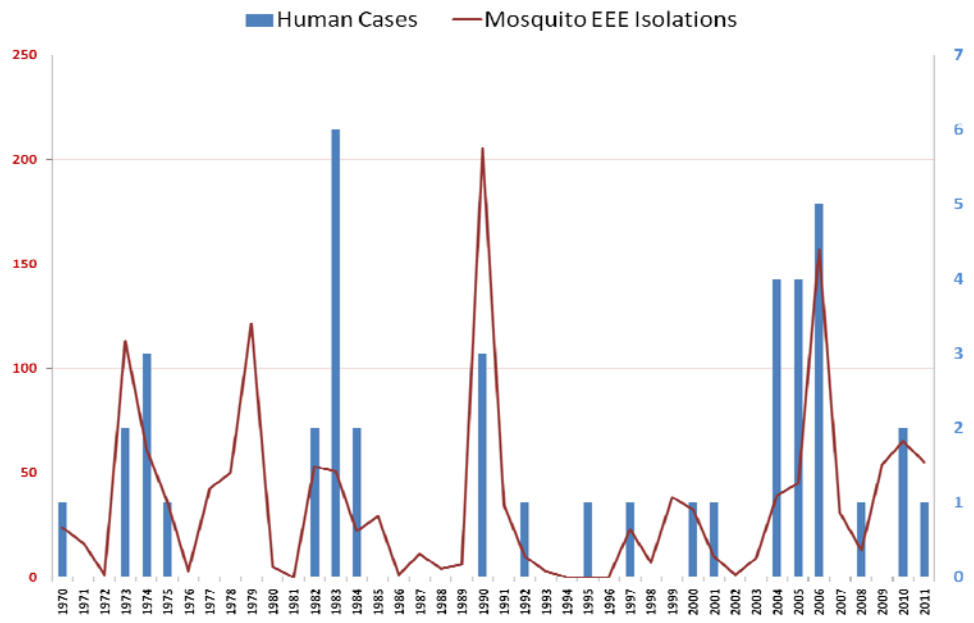


Figure 8. Mean number of *C. melanura* per trap long-term trap sites and human EEE cases, 2004-2011

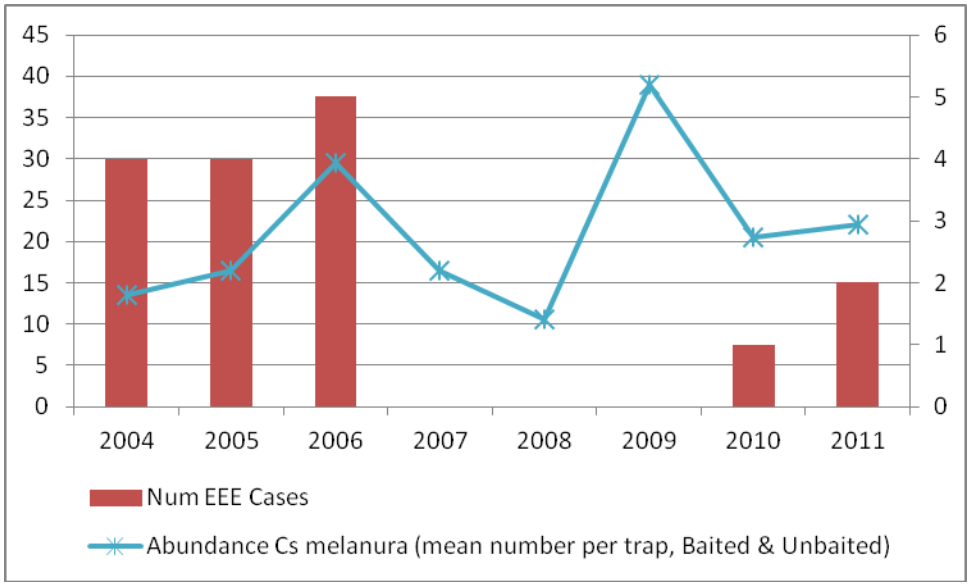


Figure 9. Abundance Infection Factor: Mean number of *C. melanura* per trap multiplied by the annual *C. melanura* minimum infection rates (MIR) from long-term trap sites and human cases, 2004-2011.

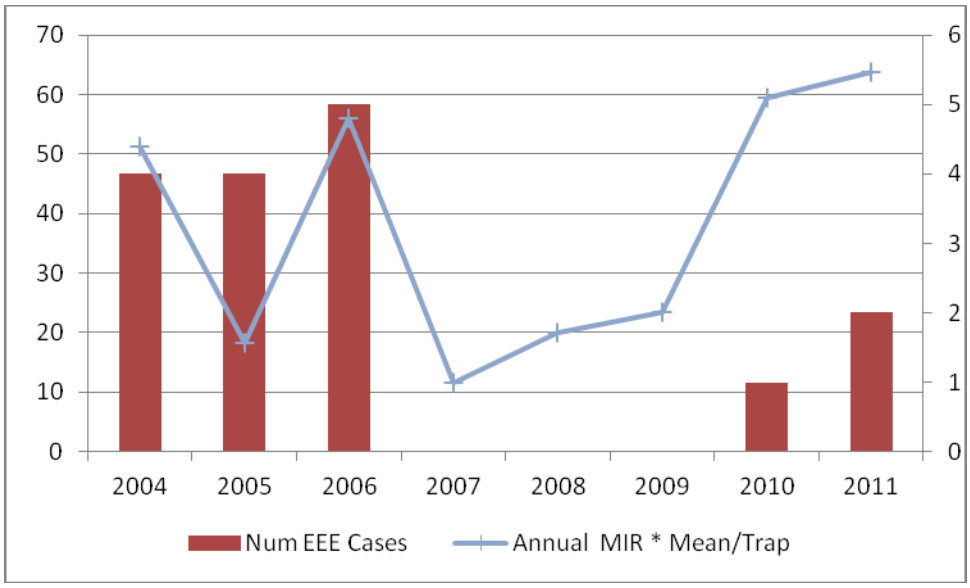
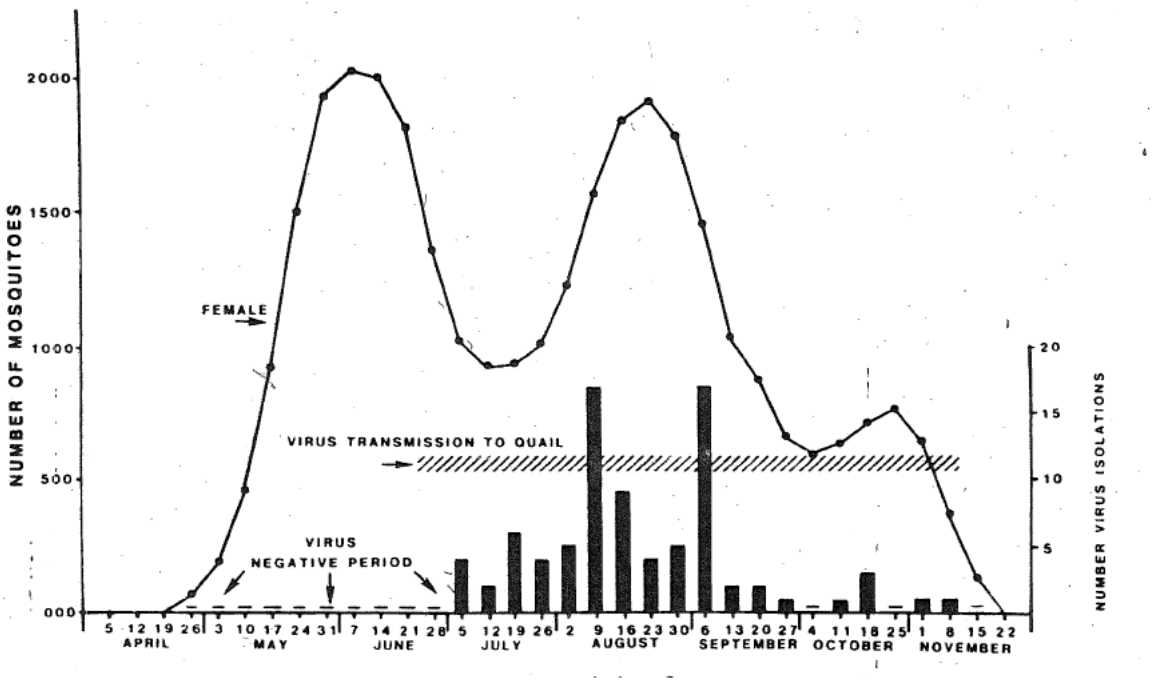


Figure 10. *Culiseta melanura* populations and evidence of EEE virus in both mosquitoes and birds by month of year (Watts, *et al.* 1982)



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