West Nile Fever

Mosquito vectors

West Nile virus is spread by bird-feeding mosquitoes in the genus Culicidae, but the virus has been found in more than 40 mosquito species. Experimental transmission of WN virus has been shown for Geliseta and Aedes mosquitoes, as has transovarial (congenital) transmission in the yellow fever mosquito (Aedes aegypti) and the Asian tiger mosquito (Ae. albopictus).

Mosquito biology

All mosquitoes lay their eggs on or near water, which is required for development of the immature stages (larva, pupa). Larvae grow to pupae in 7 to 10 days, depending on temperature, after which the adult mosquitoes emerge. Only females suck blood (Figure 3) (they start when 3 days old) but both sexes require plant sugars for sustenance. The blood is digested and used for egg development and the eggs are laid after 2 or 3 days. A wide range of aquatic habitats is used for egg laying, from water in swamps, to water in cans, cups, treeholes, discarded tires, and storm drains, to standing water in agricultural areas. Adult mosquitoes live for 2 to 4 weeks but can survive for 4 months or longer and take as many as 4 or 5 blood meals before they die.

Vertebrate hosts

Wild birds are important hosts for WN virus and infections have been detected in more than 100 avian species. Most infected birds survive, although corvids (crows, jays) frequently become ill and die. Viremia occurs in infected birds and bird migration is considered the principal means for introduction (and re-introduction) of WN virus into an area, although infection with WN virus in other vertebrates (amphibians, reptiles, mammals) is known.
WN Virus transmission cycles
West Nile virus is amplified during periods of mosquito blood feeding by the continuous transmission of virus between mosquito vectors and bird reservoir hosts. Birds can sustain an infectious viremia for 1-4 days. Most other vertebrates do not develop infectious level viremias and are “dead end” or incidental hosts (Figure 4).

West Nile virus may be transmitted through blood transfusion and recent studies have shown transmission of WN virus in recipients of solid organs from a single WN virus-infected donor. In at least one instance, transfusion of WN virus-infected blood to a nursing mother resulted in WN virus infection in the breast-feed child.

Control of mosquito vectors of WN virus
Historically, mosquito control has been accomplished using synthetic chemical insecticides. These materials continue to be the mainstay of most emergency and long-term mosquito/vector control programs. Under certain circumstances, source reduction methods that eliminate mosquito developmental sites can be used to control mosquitoes; additionally, a number of biologically-based control methods are being developed as future alternatives to insecticides.

Source reduction
Control can be achieved by discarding containers that hold water capable of producing mosquitoes (as little as 4 ml is needed), by filling/draining of pools, ponds or wetlands, and by sophisticated programs in some coastal areas that combine mosquito control with the management of tidal flow and the restoration of estuarine habitat. Source reduction methods target artificial water sources and include waste tyre disposal, management of stormwater and wastewater, and management of emergent aquatic vegetation that provides habitat for mosquito development.

Larvicides
Larvicides are natural product-based or synthetic chemical insecticides that are applied to the aquatic habitat to kill mosquito larvae. Typically, larvicides are more effective and target-specific than adulticides. Larvicides can be applied by ground or aerial application equipment and are available in many different formulations; they can be classified by mode of action as contact active, surface control agents, and natural control agents.

Contact larvicides comprise neurotoxins and toxins that affect the insect’s endocrine system. The dithiophosphate, temephos, a neurotoxin, is widely used to kill mosquito larvae. Methoprene (isopropyl (2E,4E)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate), a juvenile hormone mimic that prevents emergence of adult mosquitoes, and diflubenzuron (N-[[4-chlorophenyl]amino]carbonyl]-2,6-difluorobenzamide), a chitin-inhibitor that causes a lethal disruption of the molting process in larvae and pupae, are each active via the insect’s endocrine system.
Surface control agents include oils and ethoxylated isostearyl alcohols applied to the water surface in mosquito developmental sites. Oils suffocate larvae and pupae as they coat the insect’s internal breathing system, whereas alcohols reduce water surface tension and cause larvae and pupae to drown. Polystyrene beads have been shown to provide effective and longer-lasting larval control in urban Culex breeding sites, such as cess pits and flooded cellars.

Natural product-based larvicides include the bacteria Bacillus thuringiensis israelensis (Bti) and Bacillus sphaericus (Bs). These micro-organisms are ingested by mosquito larvae during feeding. Bacterial endotoxins released in the mosquito midgut destroy the gut wall and lead to death of the larva.

Control of Culex larvae in water retained in storm drains in urban areas of the USA has been achieved for up to 30 days using methoprene briquettes distributed by hand. Granular and liquid formulations of methoprene, Bti, and Bs, sprayed by hand or from backpacks or trucks (helicopters are used in inaccessible areas), provide control of Culex larvae for 5–30 days in wetlands, swamps, and marshes.

**Adulticides**

Control of adult mosquitoes is attained using natural product-based or synthetic chemical insecticides. These materials are applied as indoor residual sprays, as thermal fogs, as space sprays, and by ultra-low volume (ULV) aerial applications. Adulticides (mainly the pyrethroids permethrin (3-phenoxyphenyl)-methyl(+)cis-trans-3-(2,2- dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate) and deltamethrin ((s)-alpha-cyano-3-phenoxy-trans-3-(2,2- dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate) and deltamethrin (s)-alpha-cyano-3-phenoxy-trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate and deltamethrin (s)-alpha-cyano-3-phenoxybenzyl (IR, 3R)-3-(2,2-dibromovinyl)-2,2-dimethyl cyclopropanecarboxylate) are also used to treat mosquito nets. Adulticides are considered the least efficient mosquito control technique.

DDT is the only organochlorine adulticide currently in use for mosquito control. In 2000, approximately 1.2 million kg (active ingredient) was applied as indoor residual sprays for vector control. Malathion (O,O-dimethyl phosphorodithioate ester of diethyl mercaptosuccinate) and fenthion (O,O-dimethyl-O-[3-methyl-4-(methylthio)phenyl]phosphorothioate) are the most commonly used organophosphate adulticides.

Organochlorine and pyrethroid insecticides act as contact poisons and as stomach poisons. Contact activity requires penetration through the insect cuticle and causes nerve poisoning and death; stomach poisons must be ingested before they act on the insect’s central nervous system. Organophosphate and carbamate insecticides are cholinesterase inhibitors and cause paralysis in the insect.

Three pyrethroid insecticides [permethrin, resmethrin [5-(phenyl methyl)-3-furanyl]-3-furanyl 2,2-dimethyl-3-(2-methyl-1-propenyl) cyclopropane carboxylate], and sumithrin [3-phenoxbenzyl-d,1-cis,trans 2,2-dimethyl-3-(2-methylpropenyl) cyclopropane carboxylate] have been used (with piperonyl butoxide [PBO] as a synergist) to control adult Culex vectors of WN virus in urban environments, such as New York City. Two to three applications of adulticide spaced 3 to 4 days apart are needed for effective mosquito control. In some cases, however, as for vector species that are nocturnally active when aerial ULV treatments cannot be made, this treatment approach may be of limited, or no, value.

**Biological and alternative control**

The use of biological organisms (parasites, predators, pathogens) to control mosquitoes is termed biological control (or biocontrol). Biocontrol agents are host-specific, which mitigates safety concerns for non-target organisms; however, most biocontrol agents are expensive to propagate and difficult to transport/deliver in the field, thrive only within a narrow range of environmental parameters, and require periodic augmentation/reintroduction as they are not self-sustaining in the aquatic habitat. Though included earlier as larvicides (because of the endotoxins they produce), Bacillus spp. are considered biocontrol agents, as are various species of microsporidia, fungi, parasitic nematodes, predatory mosquitoes (Toxorhynchites spp.) and copepods that kill mosquitoes.

**Personal protection**

The three principal categories of personal protection are avoidance and the use of physical barriers and chemical barriers. Mosquito infested habitat can be avoided by not entering. If infested areas must be entered, the time of entry can be adjusted to avoid periods of mosquito biting activity. Loose fitting pants and shirts with long sleeves made from tightly woven fabric protect most areas of the body from mosquito bites. The head can be protected with a net and the hands with gloves. Mosquito nets and screens over windows and doors are physical barriers that prevent mosquito entry into buildings and sleeping areas. Chemical barriers include natural and synthetic repellents that are used on skin and fabric and toxicants, such as permethrin, that are applied to fabric or the fabric used to make tents, bednets, sleeping bags, ground sheets, etc.

**Natural repellents**

Pyrethrum is composed of three insecticidal esters of chrysanthemic acid (pyrethrins I) and three esters of pyrethric acid (pyrethrins II) (47). These substances have low mammalian toxicity but degrade in light and have short residual activity. Pyrethrum acts quickly on insects to cause immediate paralysis. Citronella oil contains citronellol, geraniol, and citronellol. Though widely used in commercial repellent products, citronella is less repellent to mosquitoes than dimethyl phthalate or deet. Queneling is from the waste distillate of lemon eucalyptus oil extract. The main active component is p-menthane-3,8-diol (PMD), the mosquito repellent activity of which exceeds citronella and is nearly equal to deet.

**Synthetic repellents**

Most synthetic chemical mosquito repellents have been discovered in the last-half of the 20th century. Dimethyl phthalate, dibutyl phthalate, indalone, and ethyl hexanediol are examples. Deet, developed in the 1950s, is the most...
commonly used mosquito repellent worldwide. Two additional synthetic repellents are IR 3535 (3-[N-butyl-N-acetyl]-aminopropionioic acid, ethyl ester) and KBR3023 (1-(1-methyl-propoxycarbonyl)-2-(2-hydroxy-ethyl)-piperidine). Both are effective for repelling mosquitoes, with the activity of the latter exceeding that of deet in some cases.

Repellents and toxicants on fabric
Netting jackets with hoods impregnated with deet give several weeks of protection from mosquitoes. Repellents applied to clothing usually retain their effectiveness longer than on skin because they adhere better to cotton and synthetic fibers. Mosquito nets and clothing can be treated with pyrethroid insecticides, such as permethrin, that irritate or kill mosquitoes before they can feed. Pyrethroids retain their protectant activity for several months, even after laundering, are stable in light, and are relatively safe to use.

Disease and vector surveillance and control
The objective of WN virus surveillance programs is to prevent future epidemics of WN virus. West Nile virus surveillance includes active monitoring of bird and mosquito populations, the former (in wild and sentinel birds) as an indicator of WN virus presence, the latter to detect mosquito-borne WN virus activity, to identify potential vectors, and to monitor mosquito population densities. Mosquito control is initiated in response to evidence of virus transmission. Passive veterinary and human surveillance systems are used to monitor the extent of WN virus transmission outside the bird-mosquito-bird cycle and comprise surveillance for neurologic disease in horses and other animals and surveillance for viral encephalitis in humans. The success of surveillance activities is dependent on the availability of laboratories that can provide accurate diagnostic support, including the appropriate serology and virus isolation and detection assays.

Present day vector control programs rely mainly on safe, effective, and economical chemical-based mosquito control technology. The use of this technology is constantly being challenged by natural and economic forces, such as insecticide resistance and the high development costs for new insecticides, and by societal concerns for human, animal, and environmental safety. Unfortunately, it is not possible to forecast the next mosquito-borne disease outbreak, such as WN fever, nor will new, safe, and effective vector control methods to combat such outbreaks, when they do occur, magically appear. The technology needed for this purpose must be developed now, through research. Among the critical needs, in this regard, are the development of improved vector detection and surveillance technology and new, safe, and effective chemical and alternative mosquito control methods.

Further reading and references
West Nile Story by Dickson Despommier. http://westnilestory.com/
http://www.cdc.gov/ncidod/dvbid/westnile/
http://www.westnilefever.com/
West Nile Disease brochure (can be downloaded from
http://www.niaid.nih.gov/factsheets/westnile.htm
http://www.nwhc.usgs.gov/research/west_nile/west_nile.html
http://www.cdc.gov/ncidod/dvbid/westnile/publications.htm/