In the last year, news about the Zika virus surged in the news media when the virus became associated with an increased risk of the birth defect microcephaly in Brazil. Zika virus infections have also been linked to an increase in Guillain-Barré syndrome (GBS). This lesson will help pharmacists and pharmacy technicians develop an understanding about the Zika virus and provide an overview of measures to prevent transmission. This lesson will also provide an overview of measures to control the mosquito vectors of the Zika virus.

Objectives
At the conclusion of this lesson, pharmacists and pharmacy technicians should be able to:
1. Identify symptoms of Zika virus infection.
2. Describe the known routes-of-transmission of the Zika virus.
3. Identify Zika-related complications.
4. Describe effective measures of transmission prevention and mosquito control.

Early Discovery and Characterization
There are historical data indicating that the Zika virus has been in circulation since the early 1900’s. It wasn’t until the mid 1950’s-1960’s, however, that Zika became associated with human disease. At that time the symptoms were characterized as mild and included a low fever with mild joint pain and headache to more drastic manifestations that included jaundice. The history of disease symptoms in humans remained mild through the 1980s, even though there were widespread reports of the virus in mosquito populations of Africa and Asia. Zika went largely unnoticed until 2007 when it was discovered that 73% of the population of Yap, an island in the Federated States of Micronesia, were infected. The mosquito vector was prevalent in Africa and Asia in the previous decades. These same areas also suffered from endemic infections of Dengue fever and Chikungunya which have very similar symptomatology. The Yap island outbreak is significant because it is the first wide spread outbreak of arboviral disease (carried and transmitted by an arthropod host) that was exclusively connected to Zika. The Yap islands did not have the same prevalence of Dengue fever and Chikungunya allowing the symptoms of Zika to stand out. Additionally, this is the first known event of Zika disease outside African and Asia. Up to this point, the Zika virus was considered to be solely an arbovirus and required direct contact with an infected mosquito vector to...
cause human disease. While still primarily a mosquito-borne illness, there was limited evidence in 2008 of transmission by sexual contact. A U.S. public health scientist had returned from working in Africa. His spouse, with no travel history, developed flu-like symptoms after sexual contact. This is the first known instance of any arbovirus being transmitted via sexual contact.³

**Geographic and Disease Expansion**

Until 2008, the history of the Zika virus was unremarkable, and geographically contained to continental Asia and Africa. The virus was characterized and known to cause disease in humans. However, the disease burden of the Zika virus did not cause any concern. In addition to sharing geography with regions of endemic Yellow fever, Dengue fever and Chikungunya, the Zika virus did not stand out and was relegated to the list of neglected tropical diseases. It is also likely that the overlap in symptoms with more commonly understood and more virulent arboviruses, such as Yellow Fever, caused the true disease prevalence of Zika to be under-reported. At that time, there was no inexpensive field-test to distinguish Zika from other more common and familiar arboviral infections. In addition to the evidence supporting the sexual transmission of the Zika virus, an increase in the virulence of the virus was also seen in 2008.

**Vector Expansion**

Genetically there are two major distinct types of Zika. The Asian strain and the African strain split from the original Uganda strain discovered in 1947.⁴ The number of local or regional variants will likely continue to increase as Zika continues to spread. The main mosquito vector, *Aedes aegypti*, is expanding the geographic reach of each of these viral strains due to the expansion of habitable areas. This species of mosquito is actively causing infection in Mexico, as well as in Central and South America, and now has a confirmed foothold in Southern Florida. The *Aedes* species of mosquito is not a stranger to the United States. *Ae. albopictus* is prevalent in the bulk of Gulf Coast and Southeastern U.S. The presence of the mosquito, however, does not imply rampant Zika infection. Nebraska is not in a high risk zone for the *Ae. aegypti* mosquito.⁵

**Novel Transmission of an Arbovirus**

A small number of case reports have indicated that Zika transmission is possible by exchange of any blood or body fluid. There is some evidence that Zika remains transmissible via blood or body fluids for many weeks following the resolution of acute symptoms.⁶ ⁷ A few case reports indicated that sexual contact of any variety can be a source of Zika transmission.⁸ Additionally, there is evidence to suggest that Zika can be found in breastmilk as well as in saliva, although this has not been identified as a route of transmission.⁹ Currently, the vast majority of cases of Zika in the United States are from individuals that have traveled to areas of endemic Zika infections and were bitten by a mosquito.⁸

**Complications of Zika Virus Infection**

Scientific understanding of Zika is rapidly expanding. Gaps in Zika knowledge exist, and new information about Zika continues to be published on nearly a daily basis. Zika is a public health concern due to its chief sequela, microcephaly. The neurotropic features of Zika infection should elevate some concern. The Zika virus has been directly linked to causing the microcephaly birth defect, and in some cases to causing Guillain-Barré Syndrome. Prior to 2008, there was no indication of this causality. There is also no current indication of neurological or autoimmune dysfunction directly related to Zika infection prior to 2013-2014.¹⁰ Unfortunately, it is still too early to tell what if any long term developmental, neurological, or immune system dysfunction may ultimately be linked to Zika infections of the mother or baby.

Given the current understanding and neurotropic nature of Zika, neurological disease and dysfunction secondary to Zika is no longer surprising. The two currently attributed Zika sequela carry significant morbidity. Microcephaly by itself is not a diagnosis but a feature of abnormal development of the nervous system. It is a measurement of the occipitofrontal circumference of the head that is then compared to averages in age, sex and gestation. Newborns with this feature may suffer from a range of neurological and cognitive deficits. Infectious agents such as Zika are not the only causes of this malformation. Unfortunately, microcephaly subsequent to infectious origins usually have a more negative impact on overall cognitive function and greater overall morbidity compared to chromosomal anomalies that can also cause microcephaly.¹¹ By comparison Guillan-Barré Syndrome is a diagnosis and involves mild to severe muscle weakness resulting from inflammatory nerve damage. In addition to muscle weakness, it is not uncommon for patients with GBS to also suffer from neuropathic pain similar to the pain manifestations seen in diabetic neuropathy. There is no cure, treatment, or vaccine for microcephaly. Consequently, prevention of exposure to the Zika virus is the best measure.

With the insidious modes of transmission, and the potentially disabling outcomes if infected, anything that can be done to interrupt the transmission of the Zika virus and discourage mosquito spread is paramount. Pharmacists can serve in their public health role by providing education about the prevention of viral transmission. Local, state, and national public health authorities continually monitor local mosquito populations for
disease. The Zika virus is a nationally reportable disease, and municipalities in which Zika becomes present in mosquito populations are notified. Unfortunately, mosquito surveillance is imperfect and many factors can cause lag time between discovery of Zika positive mosquito populations and dissemination of or action on that information. While pharmacists are not involved in the monitoring of mosquito populations, guiding patients towards effective mosquito repellants and home mosquito control options is important.

**Prevention: Topical Insect Repellants**

The Aedes species of mosquitoes, and specifically *Ae. aegypti*, have evolved to prefer the taste and smell of humans over other warm blooded vertebrates. The gold standard of topically applied insect repellants, N,N-Diethyl-meta-toluamide (DEET), has been shown to provide protection via two mechanisms. DEET, when applied to the skin, will start to vaporize at body temperature. The DEET vapor works against the scent tracking used by *Ae. aegypti*. The DEET film that is still present on the skin changes how humans taste to the mosquito. If the mosquito manages not to be deterred by the smell of the DEET, they will be deterred from feeding by the taste of the DEET.12

Pregnant women in the first and second trimester are at the highest risk from the Zika virus.13 When used as directed, topical insect repellants such as DEET can be used safely and effectively during pregnancy. The use of a topical insect repellent should be part of a coordinated effort of loose fitting, bright colored clothing that includes long sleeved shirts, wide brimmed hats, and pants that are tucked into footwear. These measures are especially important if travel is planned to damp or wet wooded recreational areas and other related areas where mosquitos are common. DEET comes in many different concentrations. A minimum level of 20% DEET is necessary to provide adequate protection against not only mosquitos but also ticks.

According to the manufacturers’ labeling, a 20% DEET solution applied as directed should provide about four hours of protection. Several variables, such as getting wet or profuse sweating, could necessitate reapplication sooner than four hours. The need for early reapplication of the repellant can be gauged by the early return of biting. The percent concentration of DEET does not correlate to greater repellent activity. Higher concentrations of DEET correspond to increased time between applications. The benefit of DEET is that it can be used safely by the mother in pregnancy and lactation. DEET is safe to use in infants as young as two months of age. Infants should not be exposed to DEET concentrations above 10%. Children should use DEET topically in concentrations up to 30%.14,15 Parents should be advised to never spray DEET directly into the face of children or infants. Topical insect repellant sprays may not always be desirable as they can have a peculiar odor, sticky feel, and are capable of staining some plastics and synthetic fabrics. DEET is not the only compound that is considered safe and effective as a topical insect repellent, but it does have the widest safety margin.

If the odor and feel of DEET is undesirable, another option is picaridin. The safety profile of picaridin is very similar to DEET. Picaridin may be safely used on infants and children two months of age and older. Picaridin is more potent than DEET, with concentrations of 10% providing a duration of protection that is similar to DEET at a 20% concentration.16,17

There are other alternative options for insect repellant such as oil of lemon eucalyptus oil, IR3535 (the active ingredient in Avon Skin So Soft®), wrist bands, and vitamin transdermal patches. These options have never been shown to provide adequate protection for a useful duration to be considered for this application.

Permethrin is effective but toxic and should only be applied to gear and clothing and never to the skin. DEET and permethrin have the best safety and efficacy data, and have been field tested and shown to be effective in global areas of endemic malaria with highly aggressive mosquito populations.16,17 A convenience sampling of readily available products at local merchants provided some examples of the various product lines and concentrations of DEET and picaridin and is provided above for reference.

If topical repellants remain undesirable, the list of alternative products seem to be very convincing and are heavily marketed as effective. These alternative options, including wristbands, candles and diffusers, may contain the chemicals permethrin, picaridin, or DEET, or a variety of natural oils including citronella and **

<table>
<thead>
<tr>
<th>Repellant</th>
<th>Product Name</th>
<th>Active Ingredient in %</th>
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<tbody>
<tr>
<td>DEET</td>
<td>Repel 100*</td>
<td>98.11</td>
</tr>
<tr>
<td></td>
<td>Repel Deep Wood*</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Cutter Backwoods*</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Off! Deep Woods*</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Cutter/Cutter Dry*</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Cutter Skination*</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Off! Family Care*</td>
<td>7</td>
</tr>
<tr>
<td>Picaridin</td>
<td>Sawyer Picaridin Insect Repellent*</td>
<td>20</td>
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<tr>
<td></td>
<td>Repel Tick Defense*</td>
<td>15</td>
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</tbody>
</table>
**Mosquito Repellants**

DEET is the reference agent, however, picaridin may edge DEET out in comfort.

Botanicals and derivatives can cause skin irritation and do not universally have safety data in children and infants like DEET and picaridin.

The Off!® clip-on is superior to candles for area protection. Wristbands and vitamin patches have no efficacy.

eraniol. Of the alternative products that also include coils, only personal diffuser products that actively move air around or through them showed any efficacy. The diffuser products were able to reduce landing attacks from Aedes albopictus by approximately 92% and included the metofluthrin based Off!® Clip-On diffuser. Candles provided irregular protection, and wristbands and transdermal vitamin patches provided no protection.\(^{17}\) In another study in a less controlled environment, geraniol diffusers were set approximately 20 feet from outdoor mosquito collection traps and demonstrated a 75% reduction in total female mosquito volume compared to traps that had no diffusers nearby. Citronella diffusers only reduced total female mosquito volume by 22%.\(^{18}\) Topically applied mosquito repellants still provide the best overall protection against disease carrying mosquitos. Of the alternative products, the Off!® clip-on diffuser would be useful as an additional level of area protection when used in conjunction with topical agents.

In Nebraska, mosquito season corresponds to sunscreen season. Unfortunately, the chemicals in sunscreen can cause a potentially toxic interaction when mixed with topical insect repellants. There is evidence suggesting a synergistic dermal penetration when DEET is combined with oxybenzone, a common ingredient in chemical sunscreens. Both of these substances make the skin more permeable. When used together either in a combination product or by applying two separate products at the same time, they are capable of causing measurable serum concentrations of DEET and oxybenzone in excess of either agent alone. This same study noticed that picaridin, however, did not seem to cause this enhanced permeation in combination with oxybenzone.

Consequently, picaridin may be a better candidate when both sunscreen and insect repellant would be necessary. In either case, the sunscreen should be applied first as a separate product and at least 15 minutes later the insect repellant can be applied as a separate product.\(^{19,20}\)

Insect repellants, either topical or those designed to be disseminated by a diffuser, are only part of a complete mosquito control effort. Reduction in the habitat near houses that can encourage mosquitos to move in is also necessary. The age old culprit for mosquito habitat is stagnant or standing water. Standing water in old tires is a common offender as are rain collection barrels, birdbaths, gutters that do not fully drain, and water features that allow for standing water. There is also evidence suggesting that houses in areas of lower-socioeconomic status are disproportionately rich in mosquito habitat.\(^{20}\)

The last phase of mosquito control is the use of insecticides which is saved for last because use can cause unintended ecological problems and is capable of driving insecticide resistance amongst mosquitos.\(^{21,22}\) There is also evidence suggesting that when large scale removal of mosquitos occurs, the void that is left will be recolonized quickly. While DDT was highly effective at driving *Ae. aegypti* and Yellow fever out of populated areas via mosquito eradication, its off target effects in the rest of the food chain led to unintended consequences and its subsequent ban in the United States. Several agents have emerged that target either the adult or the larval stage of the mosquito. Large scale spraying of communities has been reserved for high concentrations of infected mosquitos or neighborhoods where homeowners are unable to provide adequate control.\(^{23}\)

Providing information and counseling to women of childbearing potential and their partners, who may travel to or have contact with those who travel to areas of endemic Zika virus, is important so they can weigh risk and benefits. Urging caution about mosquito exposure or sexual contact with potentially exposed partners, especially during the first two trimesters of pregnancy, is also essential. Unprotected sexual contact with a pregnant woman also appears to be a risk factor for potentially spreading Zika to the developing fetus.

**Conclusion**

Knowledge about Zika continues to develop rapidly and the manifestations of neurological impairment, if infections occur in utero, continue to develop. Both the World Health Organization and the Centers for Disease Control continue to provide guidance as new information becomes available and is confirmed. Birth defects linked to Zika infection place additional burdens on public health agencies. Prevention of infection and reduction in mosquito habitat is critical. A multi-pronged approach that includes combinations of habitat control, topical insect repellants, and safer sexual contact are essential.
References

Zika Virus: An Emerging Arbovirus
Quiz #16, November 2016, ACPE #0128-0000-16-341-H01-P/T

1. The geographic origin of the Zika virus is?
   a. Brazil
   b. French Polynesia
   c. Tanzania
   d. Uganda

2. Symptoms of Zika infection include:
   a. Jaundice
   b. Mild headache
   c. Mild joint pain
   d. All of the above

3. The major species of mosquitoes responsible for spreading Zika is:
   a. Aedes aegypti
   b. Aedes albopictus
   c. Culex pipiens
   d. Both a and b

4. Confirmed mosquito borne transmission of Zika has occurred in?
   a. Alaska
   b. Colorado
   c. Delaware
   d. Florida

5. Current available evidence supports the following major mode of transmission of Zika:
   a. Bitten by a WNV infected Culex Pippins mosquito
   b. Bitten by a Zika infected Aedes aegypti mosquito
   c. Bitten by an uninfected Aedes aegypti mosquito
   d. Bitten by an uninfected Culex pipiens mosquito

6. Zika virus infection has been definitively linked to:
   a. Guillan-Barré Syndrome
   b. Microcephaly
   c. All of the above

7. The gold standard in chemical mosquito repellants is?
   a. DEET
   b. IR3535
   c. Permethrin
   d. Picardin

8. Of the commercially available products evaluated for use as insect repellants, _____ and _____ demonstrate the widest margin of safety and greatest overall efficacy, and can be used in infants and children as young as two months.
   a. Citronella, Gerinol
   b. DEET, IR3535
   c. DEET, Picaradin
   d. Picardin, Permethrin

9. Which of the following products provide protection from mosquitoes?
   a. Cutter Deep Woods
   b. Off! Clip-on
   c. Sawyer Picaridin Insect Repellent
   d. All of the above

10. Initial prevention of Zika virus transmission should include:
    a. Large scale community spraying campaigns
    b. Reduction in mosquito friendly habitat
    c. The use of DDT
    d. None of the above

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Keep the TOP portion for your records. Return the BOTTOM portion to the NPA office.  
Or, take this quiz online at www.npharm.org

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Name ________________________________________________________
Mailing Address  _______________________________________________
City/State/Zip _________________________________________________

*NABP e-Profile # ____________________ *Date of Birth (MMDD) _______
*Required for ACPE credit.

The deadline for this quiz is December 19, 2016

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CPE Home Study Evaluation
1. Rate this lesson:  (Excellent) 5  4  3  2  1 (Poor)
2. Did this lesson meet each of its objectives?  ____Yes ____No
3. Was the content without commercial bias?  ____Yes ____No
   If not, please explain _______________________________________
4. Did the lesson meet your educational/practice needs?  ____Yes ____No
5. Comments/future topics are welcome. ____________________________

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6 November 2016 - Bonus CPE