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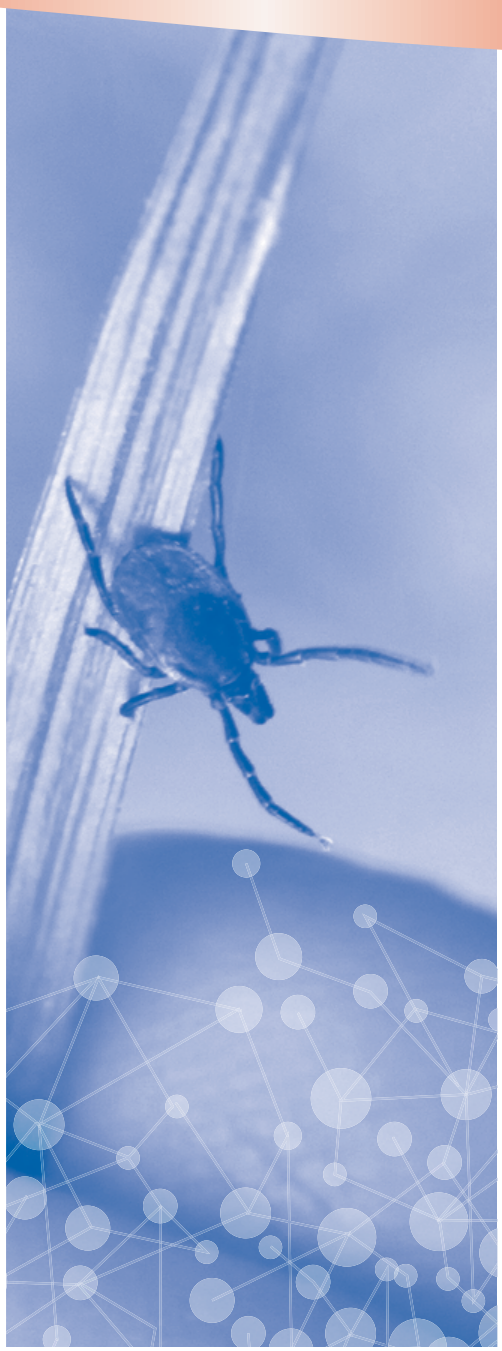
TICK-BORNE ILLNESS ISN'T JUST LYME DISEASE

A Guide to the Powassan Virus



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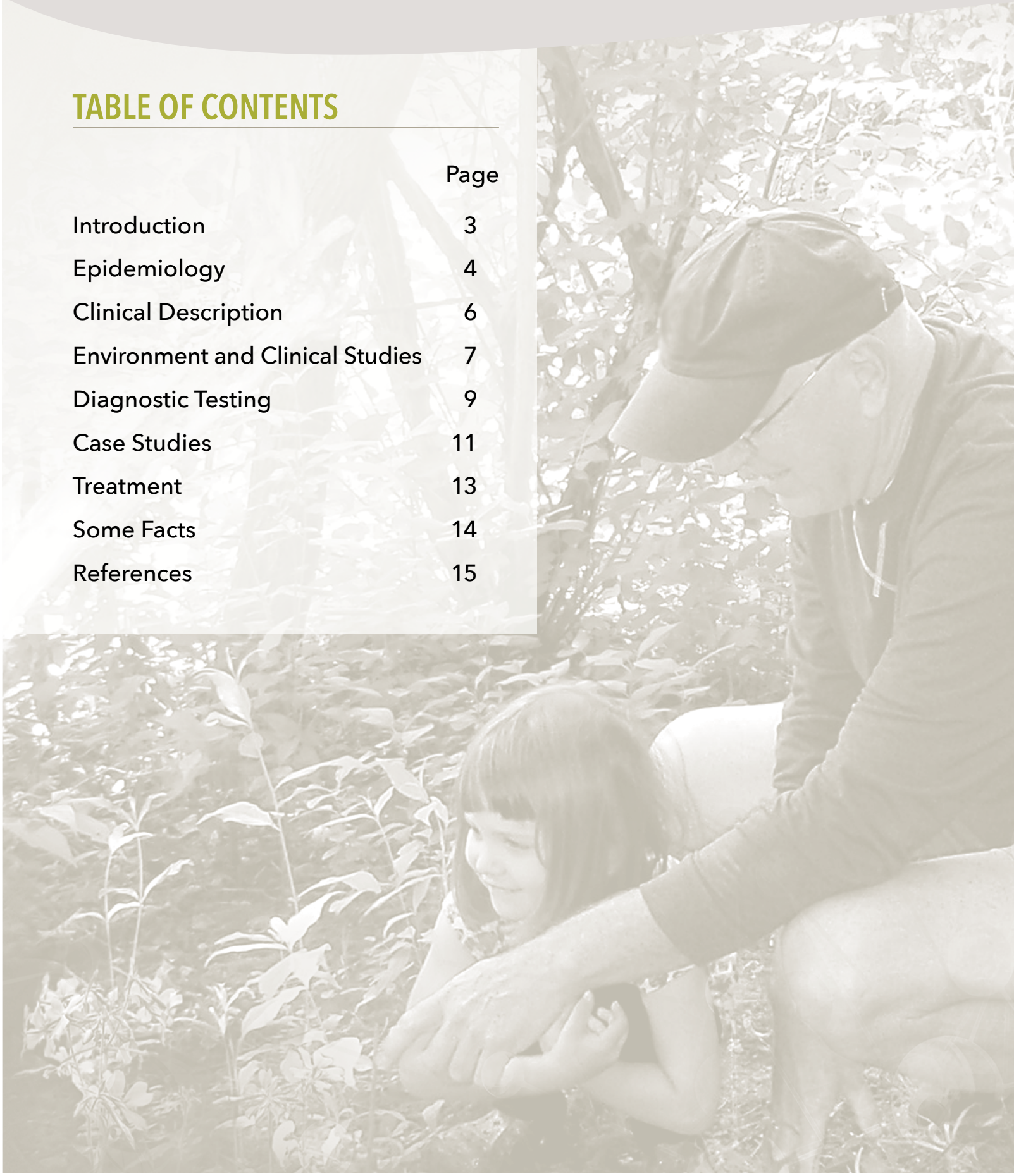
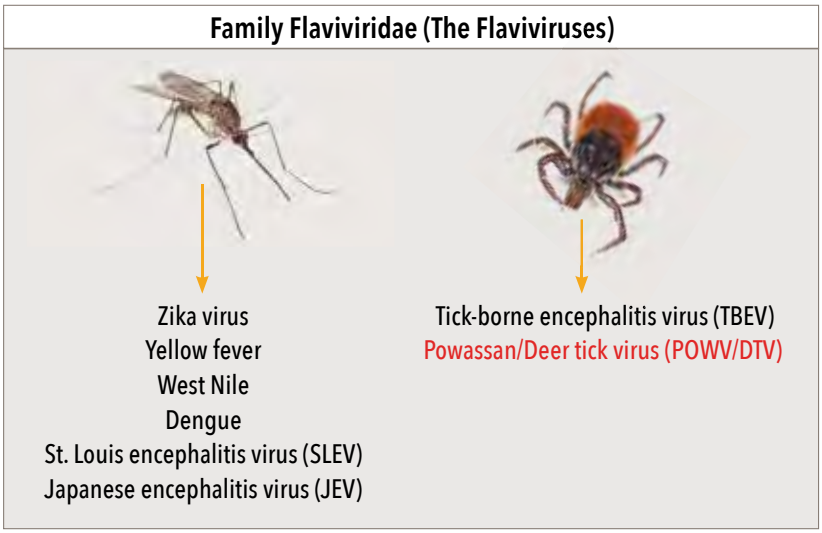


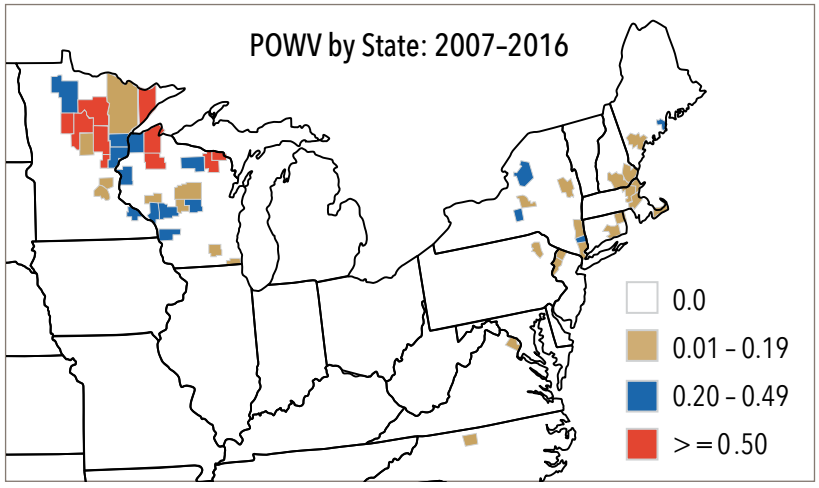
INTRODUCTION

Carried by the tick known to transmit Lyme, the Powassan virus (POWV) is a member of the family of viruses that include such familiar names as Zika, West Nile, Yellow Fever and Dengue.



Powassan is not a new virus. It was discovered in 1958 in Powassan, Ontario following the death of a five-year old boy with encephalitis.[1] It is the only tick-borne member of the Flaviviridae family known to cause human disease in North America.

Like Lyme disease, Powassan virus is expanding in the same geographic areas throughout the Northeast and Midwest United States. It is found in wooded and bushy areas as well as fields where Lyme-bearing ticks live. Experts have suggested that the virus could be a more serious threat than Lyme disease.[2]



Source: ArboNET, Arboviral Diseases Branch, Centers for Disease Control and Prevention

"Wildlife studies have shown that Powassan virus is increasing in the New England area and human case reports are increasing in the upper Midwest. As more ticks become infected with Powassan virus and more people are exposed, Powassan could become epidemic like Lyme disease. Because it can be a serious disease causing fatalities and there is no treatment, Powassan has the potential to become a greater public health concern than Lyme disease." (Durland Fish, PhD)[3]

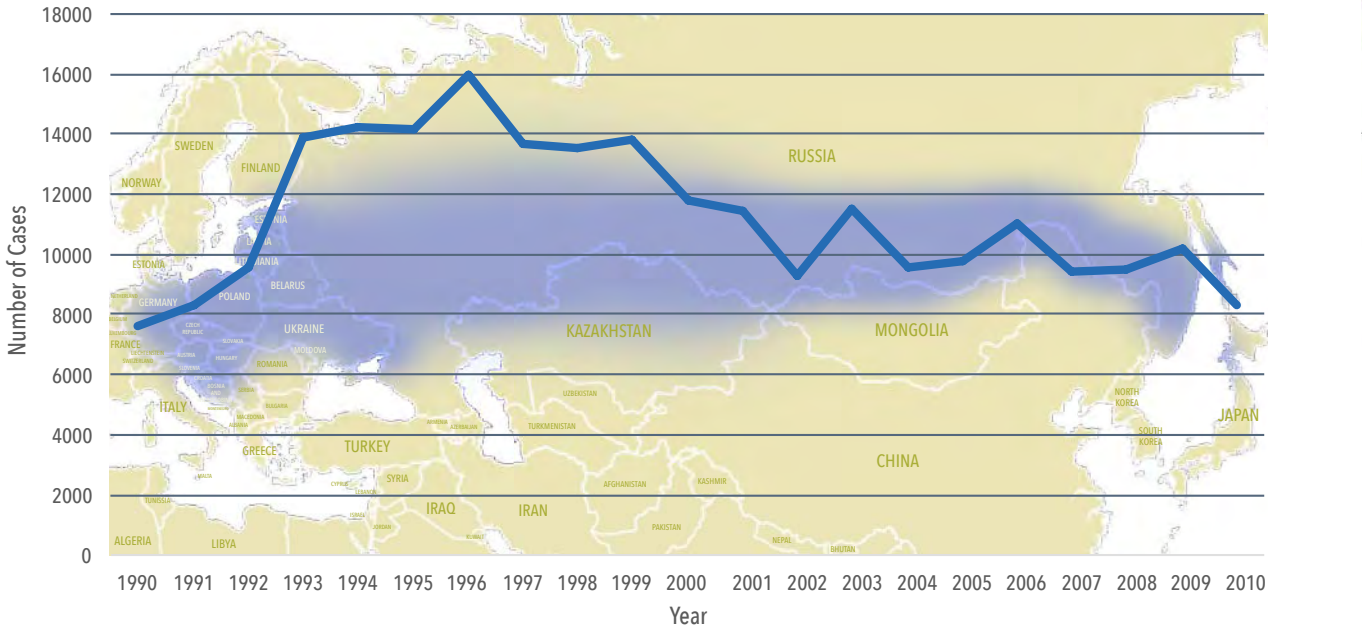
EPIDEMIOLOGY

Powassan Virus is Related to Tick-borne Encephalitis Virus (TBEV), a Health Issue in Europe

Because little research has been reported on POWV, much of the information we understand about this class of tick-borne viruses and their potential to cause illness comes from its European relative, the Tick-borne Encephalitis Virus (TBEV). **POWV and TBEV are members of the tick-borne encephalitis complex of viruses.**[4] In Europe and Asia, TBEV is a serious health issue, with 10,000–15,000 cases reported each year. The number of reported cases is increasing steadily in countries without vaccination programs.[5]

TBEV is a serious infection of the central nervous system causing thousands of hospital stays per year. With the ease of travel and the pursuit of leisure activities in endemic areas, evidence suggests infections are on the rise.[6]

TBEV Cases Reported per Year in Europe.



Experts have suggested that POWV may be on the same growth curve as TBEV was in the 1990s when some countries initiated national vaccination programs resulting in the decline seen here.

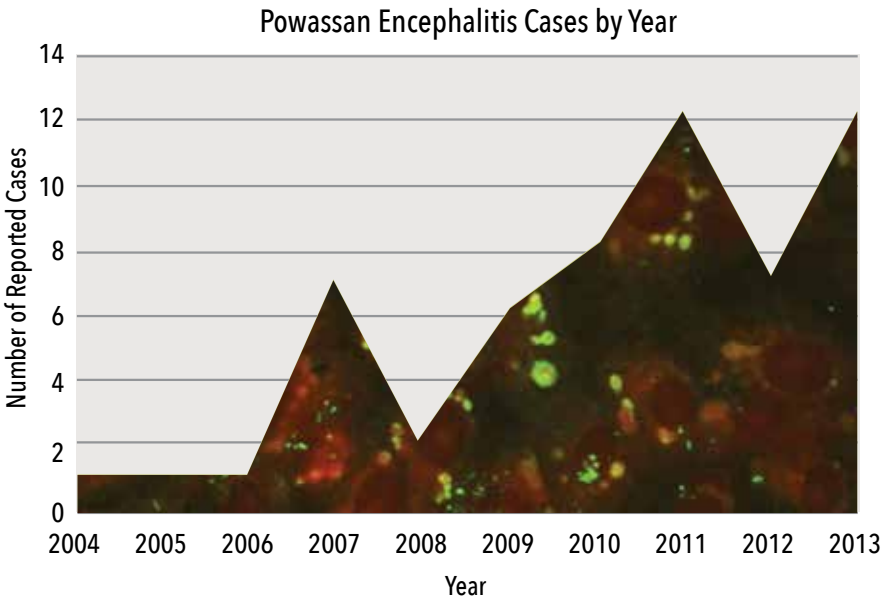
Is the Incidence of POWV in the United States Underreported?

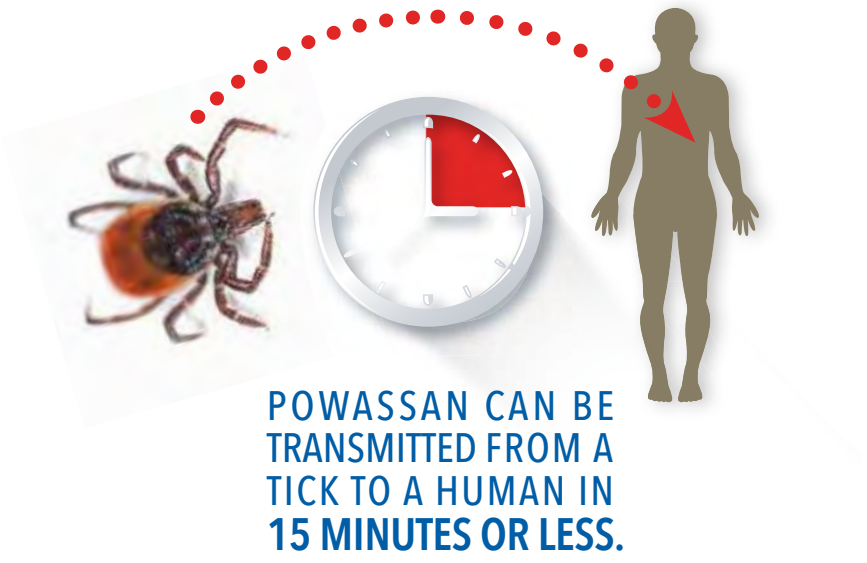
In the United States, only the severe cases of POWV are reported, thus diminishing the incidence. Despite underreporting, there has still been a 375% increase in the cases of Powassan encephalitis reported in the last five years over the previous five years.[9]

Ticks can harbor and transmit a number of pathogens – including Borrelia, POWV, Anaplasma and Babesia. Co-infection and co-transmission of more than one pathogen is common.[10]

POWV is unique among these pathogens in that transmission time from the tick to the host is 15 minutes or less, rendering tick checks less effective.

For Powassan virus, successful transmission is facilitated by factors in the tick saliva. This saliva-activated transmission makes it easier for the virus to quickly enter the host and begin replicating.[11, 12, 13]





CLINICAL DESCRIPTION

Powassan Virus Looks A Lot Like Lyme Disease

The clinical picture of POWV is similar to other tick-borne diseases, typically presenting with non-specific symptoms. Fatigue, headache, nausea and general malaise are seen within 2–7 days of exposure.

Sometimes high fevers can occur. The initial viremic stage is followed by 2–3 weeks of a symptom-free period referred to as quiescence. A significant increase in temperature after the quiescence indicates the beginning of the second stage of infection where there is often central nervous system involvement. Encephalitis can occur during this second phase.[7]

Not everyone infected with POWV experiences all of these symptoms. About two-thirds of POWV infections are sub-clinical. About 30% of symptomatic adults will contract a severe form of the disease, meningoencephalitis. One-third of these patients have incomplete recovery with neuropsychiatric symptoms that become chronic. The overall fatality rate is about 1% and severity of illness increases with the age of the patient.[8]

Because the early symptoms associated with POWV resemble those of Lyme disease, the virus may be overlooked – yet directly contribute to disease long term.

Common symptoms with POWV infection[22]

- Fever >38.0°C (101°F)
- Fatigue
- Headache
- Malaise
- Fussiness
- Listlessness
- Nausea

LYME Versus POWV

	Powassan	Borrelia
Type of Pathogen	Virus	Bacteria
Vector	Deer Tick/Blacklegged Tick	Deer Tick/Blacklegged Tick
Time from tick attachment to transmission	**15 minutes or less**	**>24 hours**
Early symptoms (7–14 days after tick bite)	Non-specific: Fever, headache, nausea, fatigue, malaise	Non-specific: Fever, headache, nausea, vomiting fatigue EM (bullseye) rash
Late or long-term symptoms	Fatigue, confusion, paralysis, speech difficulties, memory loss, encephalitis, chronic headache	Fatigue, pain, joint and muscle aches, chronic headache, sleep disturbances

ENVIRONMENTAL AND CLINICAL STUDIES

Powassan Virus in the Ticks

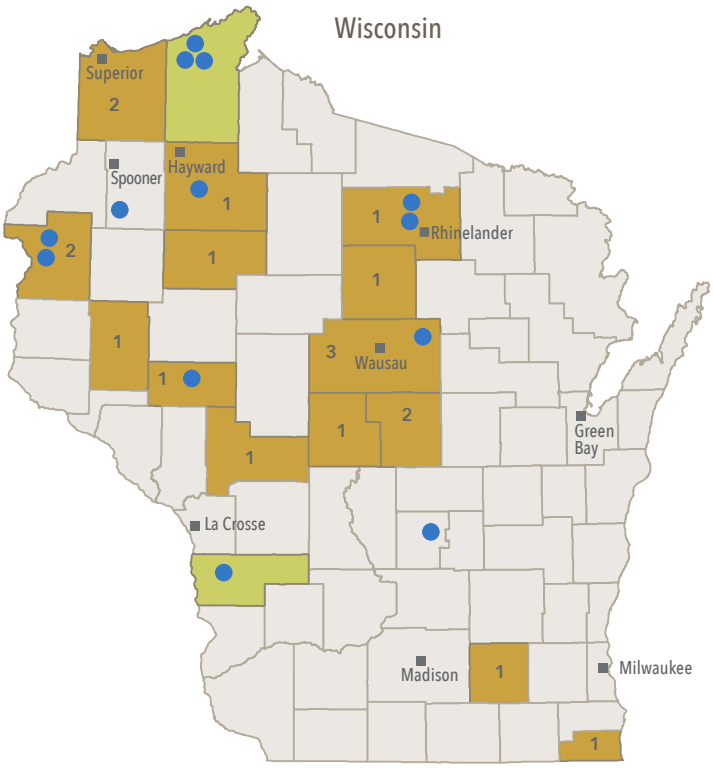
A 1999 study by Ebel et al showed that 4.6% of ticks in the upper, northwestern region of Wisconsin harbored POWV.[15] A study[17] performed by Coppe Laboratories with ticks from the same endemic area showed:

- Borrelia was detected at a frequency of 27.9%
- Powassan was detected at a frequency of 4.7%
- 50% of POWV positive single ticks were coinfected with Borrelia

TICKS CAN TRANSMIT MORE THAN ONE PATHOGEN. **POWASSAN VIRUS** SHOULD BE CONSIDERED WHEN TESTING FOR LYME DISEASE.

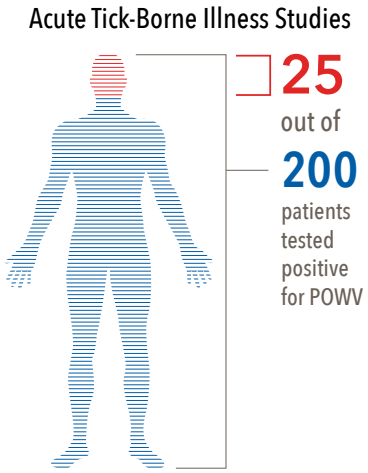
The study was particularly important because the ticks gathered were not "questing" ticks but actual ectoparasites attached to a blood host. Ticks collected were both Ixodes and Dermacentor ticks – males, females, nymphs and eggs. Ixodes ticks carried both Borrelia and POWV, and Dermacentor ticks also carried Borrelia. The authors concluded that further investigation is needed to determine if Dermacentor ticks transmit infection to humans. Currently the Ixodes tick is considered the sole vector for Lyme and POWV.

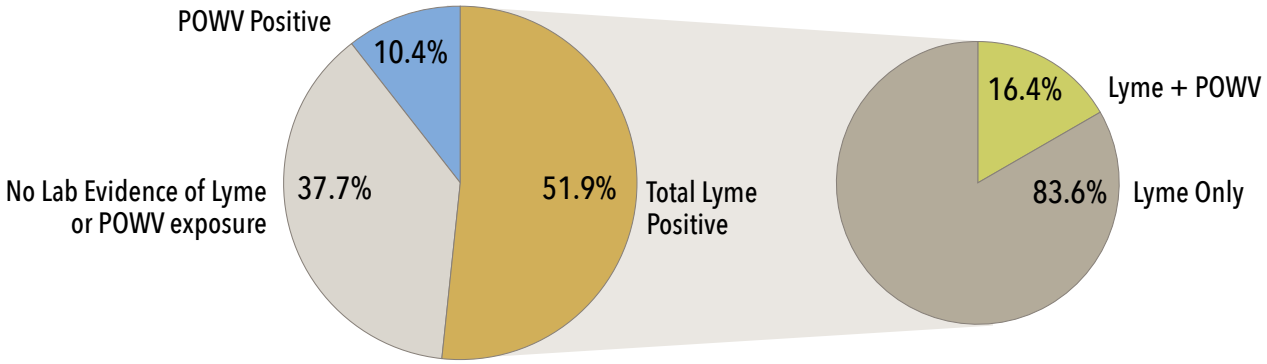
In these studies, Coppe Laboratories showed that the distribution of POWV positive ticks closely mirrors the counties reporting POWV exposure.



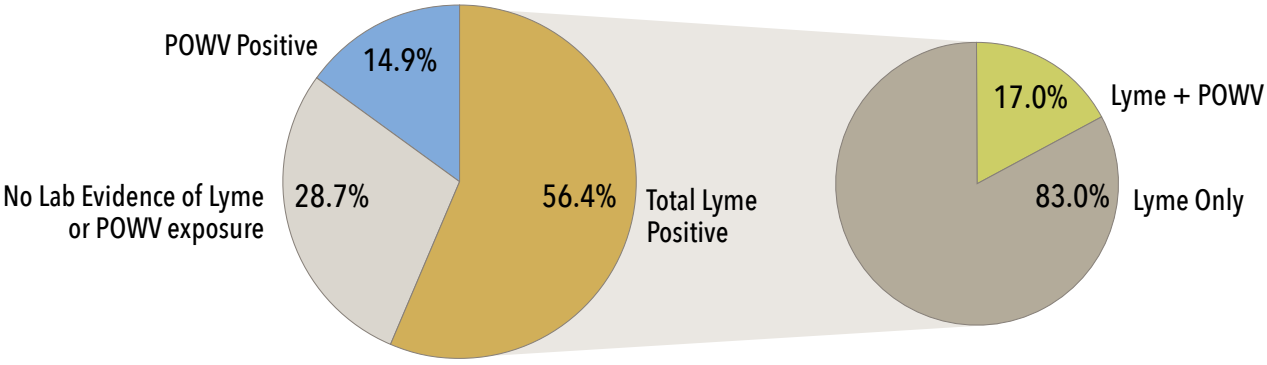
Incidence of Powassan Virus in Acute Tick-borne Illness Samples

In 2016, Coppe Laboratories' Study 1 evaluated 106 patients with suspected acute tick-borne disease and 10.4% tested positive for POWV by immunofluorescence assay. Nearly 17% of the patients with positive Lyme results also tested positive for POWV exposure. The authors concluded, "Infection with POWV may be underdiagnosed and may contribute to the persistent symptoms often associated with Lyme disease diagnosis."[16]





Study 2 was performed in 2017, when 94 additional samples were tested for Lyme and POWV. POWV exposure was detected in 14.9% of these samples, and again 17% of the patients with positive Lyme results also tested positive for POWV.



In both studies, the percentage of Lyme patients co-infected with POWV was about 17%, coinciding with the 10 – 20% of patients treated for Lyme that develop lingering symptoms attributed to post-treatment Lyme disease syndrome.

DIAGNOSTIC TESTING

Direct Testing: **Powassan RT-PCR**

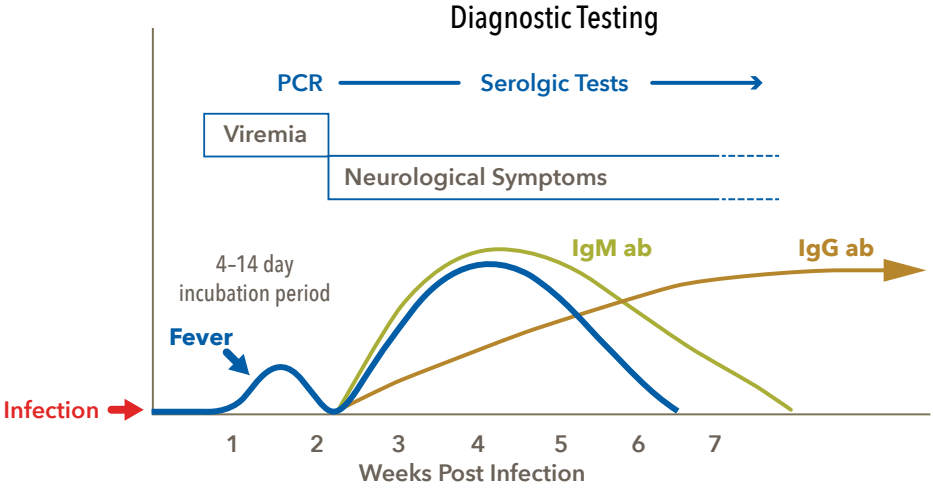
- Measurement of the actual viral RNA genome
- Most sensitive during acute infection in patients experiencing symptoms for less than six weeks

Indirect Testing: **Powassan Serology**

- Measurement of patient's antibody response to the virus
- Detects IgG and IgM antibodies specific for Powassan virus
- Results help determine the stage of infection including chronic disease

Who should be tested for POWV?[16]

- Patients with a recent tick bite. Studies have shown 2–9% of ticks to be infected with POWV in Lyme endemic areas.[17]
- Patients with Lyme or another tick-borne illness who have been treated with antibiotics and have persistent symptoms consistent with post-treatment Lyme disease.
- Patients with tick exposure who have tested negative for Lyme disease or other tick-borne illnesses who continue to have symptoms.
- Patients with tick exposure and unexplained neurologic symptoms.
- Chronic Fatigue Syndrome (CFS) or Post-Infectious Fatigue (PIF) patients with tick exposure.



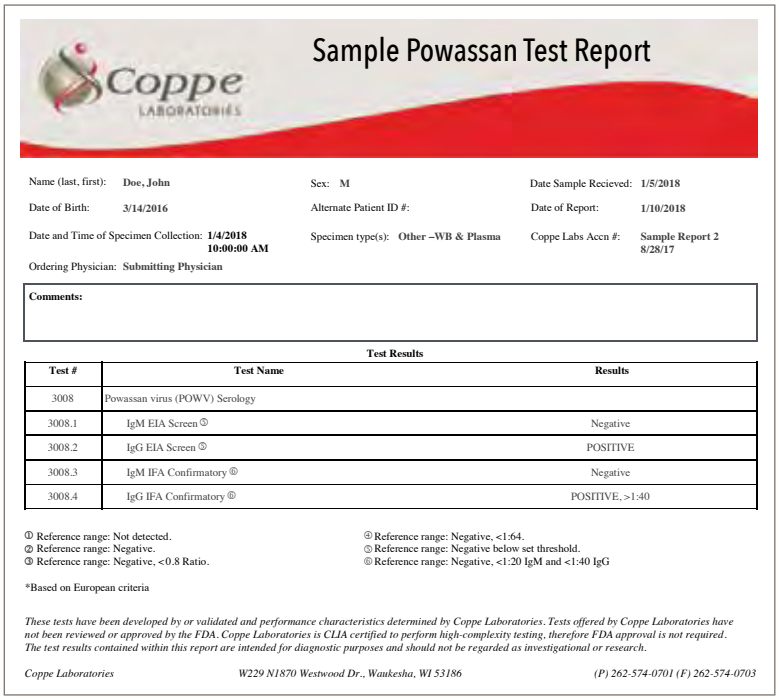
PCR=polymerase chain reaction
Serologic Tests: IgG and IgM

Holzmann, H; *Vaccine 21* (2003)

The PCR or direct test measures viral RNA and will be positive in the first 4 weeks after symptoms occur. Neurological symptoms appear around 2 weeks after the tick bite and can include confusion, speech difficulties, stiff neck and memory loss. At about 4 weeks post tick bite, the serology tests, will become positive.[14]

Testing for Powassan Virus by Coppe Laboratories

Until recently, laboratory testing for Powassan virus has been limited to the Centers for Disease Control (CDC) and a few state laboratories. Coppe Laboratories, a high-complexity CLIA-certified diagnostic laboratory, has developed both direct and indirect tests for Powassan virus. **Coppe Laboratories is the only commercial laboratory to offer this testing.**



Sample Powassan Test Report

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Name (last, first): **Doe, John** Sex: **M** Date Sample Recieved: **1/5/2018**

Date of Birth: **3/14/2016** Alternate Patient ID #: Date of Report: **1/10/2018**

Date and Time of Specimen Collection: **1/4/2018 10:00:00 AM** Specimen type(s): **Other –WB & Plasma** Coppe Labs Accn #: **Sample Report 2 8/28/17**

Ordering Physician: **Submitting Physician**

Comments:

Test Results

Test #	Test Name	Results
3008	Powassan virus (POWV) Serology	
3008.1	IgM EIA Screen ③	Negative
3008.2	IgG EIA Screen ①	POSITIVE
3008.3	IgM IFA Confirmatory ⑥	Negative
3008.4	IgG IFA Confirmatory ⑥	POSITIVE, >1:40

① Reference range: Not detected.
② Reference range: Negative.
③ Reference range: Negative, <0.8 Ratio.
④ Reference range: Negative, <1:64.
⑤ Reference range: Negative below set threshold.
⑥ Reference range: Negative, <1:20 IgM and <1:40 IgG

*Based on European criteria

These tests have been developed by or validated and performance characteristics determined by Coppe Laboratories. Tests offered by Coppe Laboratories have not been reviewed or approved by the FDA. Coppe Laboratories is CLIA certified to perform high-complexity testing, therefore FDA approval is not required. The test results contained within this report are intended for diagnostic purposes and should not be regarded as investigational or research.

Coppe Laboratories *W229 N1870 Westwood Dr., Waukesha, WI 53186* *(P) 262-574-0701 (F) 262-574-0703*

Interpretation of RT-PCR Results

Direct Test	Result	Interpretation
RT-PCR	Not detected	No viral RNA detected in the blood. Viremia may be transient; therefore this test does not rule out POWV infection.
	Detected copies/mL and log copies/ml	Viral RNA detected in blood (viremia). Suggests active POWV infection.

Interpretation of Results of the Serology Test – Both IgG and IgM Reported as Positive or Negative

IgG antibody	IgM antibody	Interpretation
Negative	Negative	No detection of POWV-specific antibodies. In the case of continued clinical suspicion, suggest retesting after 2-4 weeks (possibility of delayed antibody formation). This result does not exclude the possibility of POWV infection. Patients in early stages of infection may not produce detectable antibodies.
Negative	Positive	Detection of IgM antibodies to POWV in the absence of IgG antibodies typically indicates early-stage infection. However, IgM antibodies induced by flaviviruses may persist in the serum for 12 months or more* and therefore do not always indicate an acute infection.
Positive	Negative	Detection of IgG antibodies to POWV in the absence of IgM antibodies likely indicates past exposure at an undetermined time.
Positive	Positive	Detection of specific IgG and IgM POWV antibodies indicates recent, active infection. Persisting IgM antibodies from past infections may occur.

*IgM antibodies induced by flaviviruses, such as TBEV and WNV, are known to persist in serum and CSF for 12 months or more (Kapoora et al., 2004; Stiasny et al., 2012). IgM antibodies against TBEV persisted for up to 32 months following infection (Stiasny et al., 2012). In addition, anti-WNV IgM antibodies persisted for up to 16 months in previously exposed blood donors (Busch et al., 2008; Prince et al., 2008).

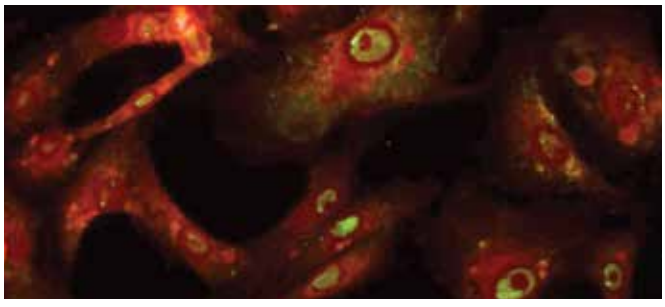
CASE STUDIES

Case Study 1:

A 60-year old male with a recent history of tick bite went to his doctor after complaining of weakness, headaches and fever. Initially he was treated with doxycycline for Lyme disease. After 14 days of therapy, he continued to have fevers, was weak and had difficulty walking.
At the insistence of his wife, he went to the emergency room when his temperature rose to 101.8°F. He was empirically treated with IV doxycycline and was admitted to the hospital.

Initial tick-borne disease testing included Lyme serology, which was non-reactive. Tests for Anaplasma, Babesia and West Nile virus were also negative. His fever persisted and he continued to complain of generalized weakness. A POWV PCR and antibody panel was ordered. RT-PCR showed 4.5 log copies/mL (whole blood) and the IgM antibody was positive (3 weeks after presentation). Knowledge of the presence of the virus resulted in discontinuation of antibiotics and induction of supportive measures. The patient gradually recovered some strength and improved neurologically. Three months after his hospitalization he continued to have periods of confusion and weakness.

This case represents an acute POWV infection with long-term neurologic manifestations.



Immunofluorescent antibody (IFA) test demonstrating the presence of Powassan antibodies in a patient sample.

Case Study 2:

A 69-year old male with a history of tick bite was evaluated at a local emergency room for progressive weakness, headache and fever. He was diagnosed with a urinary tract infection and was treated with ciprofloxacin. He continued to have fevers and progressive weakness with difficulty walking. He described difficulty in controlling the movement of his limbs. He returned to the emergency room when his temperature rose to 100.4°F and his weakness was markedly pronounced. His neurological examination was suggestive of non-focal, generalized weakness but without any loss of muscle power.

An initial infectious disease work up included:

- Anaplasma/Ehrlichia serology for IgG: negative
- Anaplasma/Ehrlichia PCR: negative
- West Nile IgM: negative
- Babesia IgM: negative
- Babesia PCR: negative
- Lyme serology: negative

He was empirically treated with IV doxycycline. He continued to have fevers during his admission. The POWV antibody panel was eventually ordered. IgM for POWV was positive. The patient remained in the hospital for several days. His condition gradually improved and strength returned. He was discharged to a skilled nursing facility for further rehabilitation. He continued to improve neurologically. At his last follow-up, 4 months after his hospitalization, he continued to have some muscle weakness particularly in his quadriceps. His range of motion in the knee joint was also restricted.

Case Study 3:

A woman in her late fifties was bitten by a tick sometime during an eight-day camping trip in northern Wisconsin. After a few days of dizziness, non-productive cough and fear of noise, she went to the local emergency room. An acute fever (102.2°F) accompanied by severe headache and muscle pain prompted her admission to the hospital. Muscle weakness, nausea and vertigo were also present. On clinical examination no neurological abnormalities were detected. On the right buttock there was a red induration of 1 cm in diameter at the location of the tick bite. During the ten days of admission, headache and muscle pain were the main complaints. Lyme serology was negative. Early phase POWV infection was suspected based on the clinical picture (fever and headache) in combination with the history of a tick bite and the recent leisure activities in a POWV endemic area. PCR on a plasma sample taken four days following onset of disease showed POWV RNA and POWV IgM antibody testing was positive, confirming an acute POWV infection. The patient recovered gradually. One month later she had only mild headaches and hypersensitivity to noise.

"Our hypothesis is that some patients with ongoing symptoms who have not responded to antibiotics known to be effective against Borrelia may be infected with viruses or other antibiotic resistant bacteria."

– Ian Lipkin, MD; Columbia University Press Release, February 16, 2016

TREATMENT

Powassan Virus Treatment

Currently there are no medications or vaccines for Powassan virus and antibiotics are not effective. Many physicians recommend immune system boosters to provide the patient with natural defenses to manage and alleviate symptoms. When the conditions are severe and warrant hospitalization, treatment may include respiratory support, intravenous fluids and medications to reduce swelling in the brain.

Co-infections Might Necessitate Extended Antibiotic Therapy When Powassan is Involved.

- Viruses belonging to the same family as Powassan are known to inhibit immune function and interfere with a patient's ability to defend against other invading pathogens.[19]
- Patients with co-infections may benefit from extended antibiotic therapy following acute infection.[20, 21]
- Immune modulatory drugs such as interferons may be a future treatment option.

"Humanity", a soapstone carving. Gift to Coppe Healthcare Solutions from the people of Kisii County, Kenya.

"You can get seizures, high fevers and stiff neck. It comes on so suddenly that it's the kind of thing people go to the emergency room for."

– Daniel Cameron, MD; CBS NY, April 2015

SOME FACTS

Some Facts About Powassan Virus (POWV)

- The Powassan virus incubation period (time from tick bite to onset of symptoms) ranges from one week to one month.
- Common symptoms include fever, headache, fatigue, weakness, confusion and malaise. In more serious cases, seizures, speech difficulty and loss of coordination can occur.
- POWV can infect the central nervous system, resulting in severe neuroinvasive disease: encephalitis and meningitis.
- About 50% of patients with encephalitis have permanent neurological symptoms, such as recurrent headaches, muscle weakness and memory problems.
- Approximately 10% of POWV encephalitis cases are fatal.
- Antibiotics are ineffective.
- POWV is carried by the same tick that transmits Lyme disease, Babesiosis and Anaplasmosis.
- Co-infection with Powassan and Borrelia may warrant more aggressive antibiotic therapy.

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