

Ecology of Powassan Virus in the United States

Subjects: **Virology**

Contributor: Saravanan Thangamani , Erin Hassett

The Powassan virus (POWV) is a rare tick-borne virus that can cause severe neurological damage and death, and the incidence of the associated disease (Powassan virus disease) is increasing in the eastern United States. The mechanisms by which POWV is maintained in nature and transmitted to humans are complex and only partly understood.

powassan virus

deer tick virus

ticks

tick-borne virus

1. Introduction

POWV is a neuroinvasive, single-stranded, positive sense RNA tick-borne flavivirus (*Flaviviridae*), and it is the only member of the tick-borne encephalitis serogroup in North America. POWV was first isolated in 1958 from the brain of a five-year-old boy from Powassan, Ontario who died of encephalitis (Figure 1) [1]. In 1970, the first human case of POWV in the US was reported in New Jersey (Figure 1) [2]. Approximately two decades later, a tick-borne encephalitis-like virus was detected in *Ixodes scapularis* (deer ticks) which was genetically different than POWV and thus was named deer tick virus (Figure 1) [3]. Subsequently, it was discovered that POWV had two lineages: Powassan virus lineage I (POWV-LB), isolated from the first case, and Powassan virus lineage II (DTV) isolated from *I. scapularis* ticks [3]. While the two lineages share 84% nucleotide identity and 94% amino acid sequence [4], they are serologically indistinguishable [5] and are both diagnosed as Powassan virus.

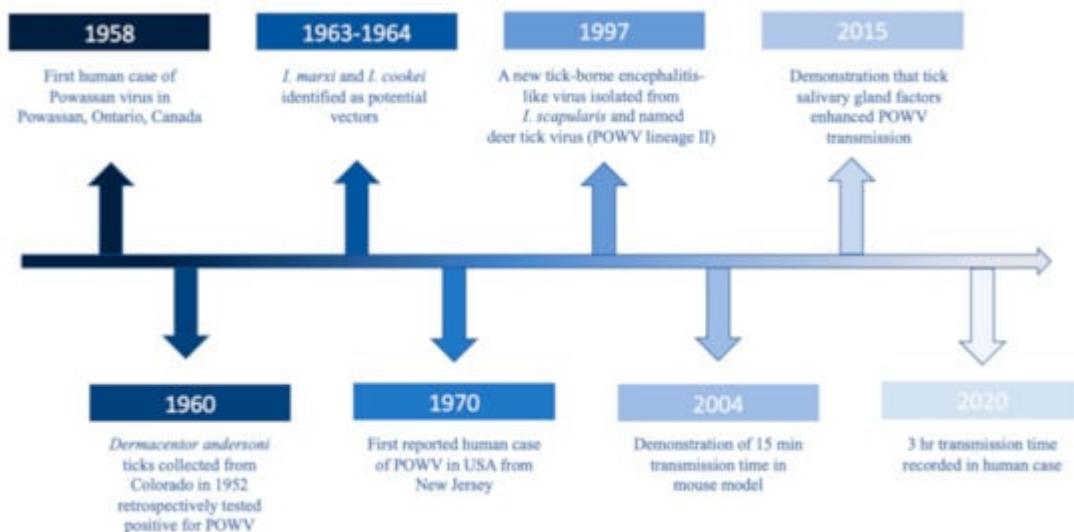


Figure 1. Timeline of major POWV milestones.

Clinical cases of POWV are defined by the CDC as having a fever, central and peripheral nervous system dysfunction, and the absence of a more likely clinical explanation [6]. Human cases are restricted to the distribution range of the tick vector, namely in the Northeast and Upper Midwest states, and they are rising in incidence (**Figure 2**). Prior to 2006, only 20 cases were reported to the CDC [7]. However, between 2010 and 2019 alone, 181 cases were reported [8]. This increase is likely due to increased surveillance and reporting (POWV neuroinvasive and non-neuroinvasive diseases were added to the list of nationally notifiable diseases in 2001 and 2004, respectively), improved diagnosis, and/or increased prevalence [7][9]. With POWV disease being a rare tick-borne disease that can also have non-specific symptoms, it is likely that cases are underestimated and/or misdiagnosed, and the true extent of the case geographic distribution cannot be determined [10].

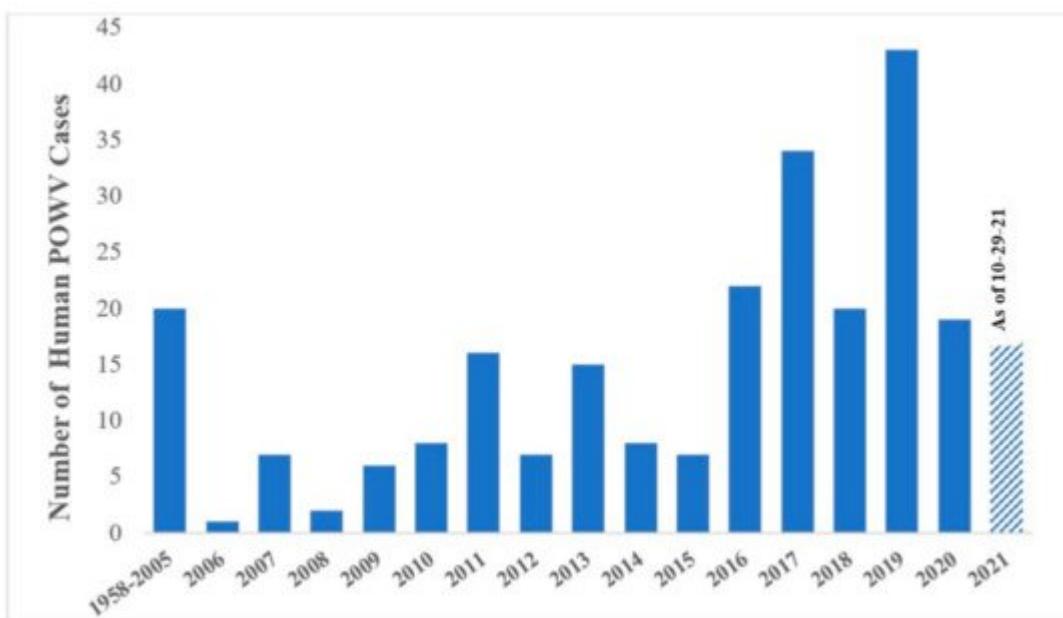


Figure 2. The number of human POWV cases reported from 1958–2021. From 1958–2005, only 20 cases were reported. From 2006–2020, an average of 14 cases a year were recorded [7][11]. Data for 2021 is represented up to 29 October 2021.

Unlike *B. burgdorferi*, POWV can be deadly, with a 3–35.7% case fatality rate and long-term neurological damage in 50% of survivors [10][12]. Importantly, both strains of the virus can cause fatal neurological disease [12][13], and common symptoms can include encephalitis, meningitis, aseptic meningitis, febrile illness, lethargy, weakness, confusion, headaches, and vomiting [7][14].

2. Vector and Host Associations

After the first fatal case of POWV, targeted field investigations looked towards ticks as the vector since POWV is serologically related to Russian spring-summer encephalitis virus, a known tick-borne virus [15]. Unsurprisingly, researchers did discover that Ixodid ticks were responsible. POWV-positive *Ixodes marxi* (squirrel tick) were

collected from a red squirrel (*Tamiasciurus hudsonicus*), and the virus was isolated from the blood of another squirrel, suggesting a potential enzootic cycle for POWV (Figure 1) [16].

A number of field-collected vertebrates were found with neutralizing antibodies for POWV, indicating prior infection, including striped skunks, short-tailed and long-tailed weasels, raccoons, porcupines, red squirrels, gray squirrels, groundhogs, opossums, some birds, and chipmunks [9][16][17][18][19][20].

While the enzootic cycles sustaining POWV-LB are purported to be between *I. cookei* and groundhogs and mustelids, and, to a lesser extent, *I. marxi* and squirrels, conclusive evidence for a wildlife reservoir of DTV is lacking. It is known that larval and nymphal *I. scapularis* frequently parasitize white-footed mice (*Peromyscus leucopus*) in the US, and this vector-host relationship robustly sustains *B. burgdorferi* in nature. It is often assumed in the literature that *P. leucopus* is also the reservoir for DTV. One study found seropositive wild-caught *P. leucopus* and DTV-infected *I. scapularis* in the same site, but the seroreactivity could have been from either POWV-LB or DTV [21]. Two *Peromyscus* spp. also had DTV antibodies in New Mexico, but this could not be confirmed in the absence of any vectors, isolates, or sequence data [22].

It is possible that potential reservoirs for DTV are small burrowing rodents such as voles because, unlike *B. burgdorferi*, DTV appears focally, even though it is transmitted by the same vector species. Because DTV is understudied, a lot of what is known is extrapolated from our knowledge about tick-borne encephalitis virus (TBEV), a flavivirus closely related to POWV that circulates in Europe. Specifically, POWV and DTV are members of the TBEV complex. In Europe, there is strong evidence that voles (*Myodes* spp.) are the natural reservoirs for TBEV. TBEV was isolated from the brain of voles in Slovakia [23] and from the spleen, lung, and kidney in wild voles in the Czech Republic [24].

3. Transmission Dynamics

As with other tick-borne viruses, multiple modes of transmission exist for POWV (Figure 3). Since both lineages are so similar, it can be expected that transmission mechanisms are likely the same.

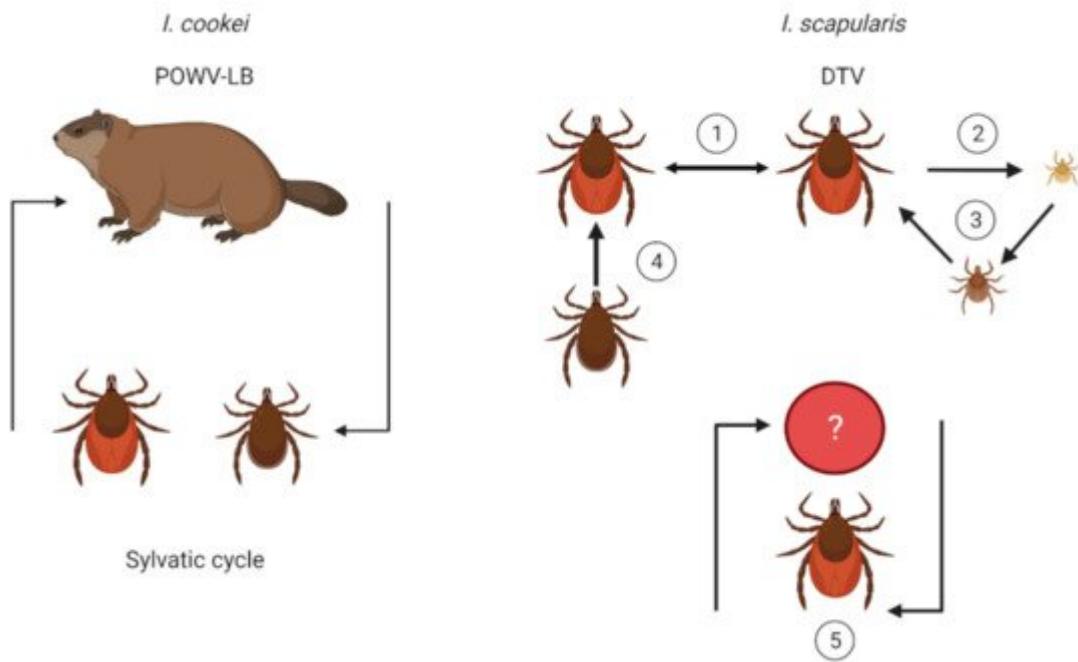


Figure 3. Transmission dynamics of POWV in *I. cookei* and *I. scapularis*. The maintenance of POWV-LB is purported to be between groundhogs and *I. cookei*; however additional mechanisms of transmission may exist, similar to DTV. *I. scapularis* may maintain DTV in nature through (1) cofeeding on a host, irrespective of host viremia, (2) vertical transmission, (3) transstadial transmission, (4) venereal transmission, and (5) a sylvatic cycle with an unknown reservoir. Illustrations were created using Biorender (biorender.com, accessed on 30 September 2021).

Concerningly, a unique feature of POWV is that it can transmit to the mammalian host in as little as 15 min of tick attachment [25], compared with *B. burgdorferi* which transmits between 24–48 h [26]. While this transmission study occurred in a mouse model, human cases have been found to occur with tick attachment in as little as 3–6 h [27]. The quick dissemination from tick to host may occur since POWV virus is already present in the salivary glands prior to the acquisition of the next blood meal [25], as opposed to the *B. burgdorferi* spirochete which is housed in the midgut before migrating to the salivary glands [28]. Furthermore, it has been shown that tick saliva enhances POWV transmission (Figure 1) [29]. Due to the rapid transmission rate and lack of grace period for tick removal, POWV has a high potential for causing disease in humans, exacerbated by the fact that nymphs can transmit the virus and are less detectable because of their small size. POWV also transmits transtadially [25][30], and there is minor evidence of vertical transmission to offspring [30]. However, more confirmatory research is needed. Venereal transmission may also facilitate transmission if the infected saliva from a male coats the spermatophore during transfer to an uninfected female [30]. Furthermore, some evidence has been shown for the transmission of POWV through infected milk [31], and this has also been demonstrated for TBEV transmission [32][33].

4. Spatial, Temporal, Habitat, and Meteorological Associations

Since POWV is maintained in nature by Ixodid ticks, the presence of POWV depends on the geographic location where the vectors are found and suitable environmental factors that support the vector population. With transmission cycles primarily sustained by *I. cookei* and *I. scapularis*, discussions of environmental associations will focus on these two species. However, compared to *I. scapularis*, research on *I. cookei* is sparse since it historically is encountered less by the public. *I. scapularis* and *I. cookei* are found throughout the eastern half of the US, with concentrations in the Northeast, Upper Midwest, and Great Lakes regions, and the distribution range is expanding [34][35][36]. *I. scapularis* has a larger distribution range compared to *I. cookei*, which may assist its ability to vector POWV more effectively to a larger population.

The seasonality of tick life stages influences transmission potential since, during periods of host-seeking activity, ticks actively bite and pass the virus to hosts. *I. scapularis* has a two-year life cycle where adult ticks quest in spring and late fall (March–April; October–November), nymphs in early spring (June–July), and larvae in early fall (July–August; **Figure 4**) [37]. Comparatively, *I. cookei* activity occurred all year, with nymph and adult activity peaking in July while larvae activity showed fluctuations from March through December [34]. In the interim, the tick is dormant while digesting and molting into the next life stage. Consequently, human cases of POWV disease coincide with tick activity (i.e., late spring, early summer, and mid-fall) [38].

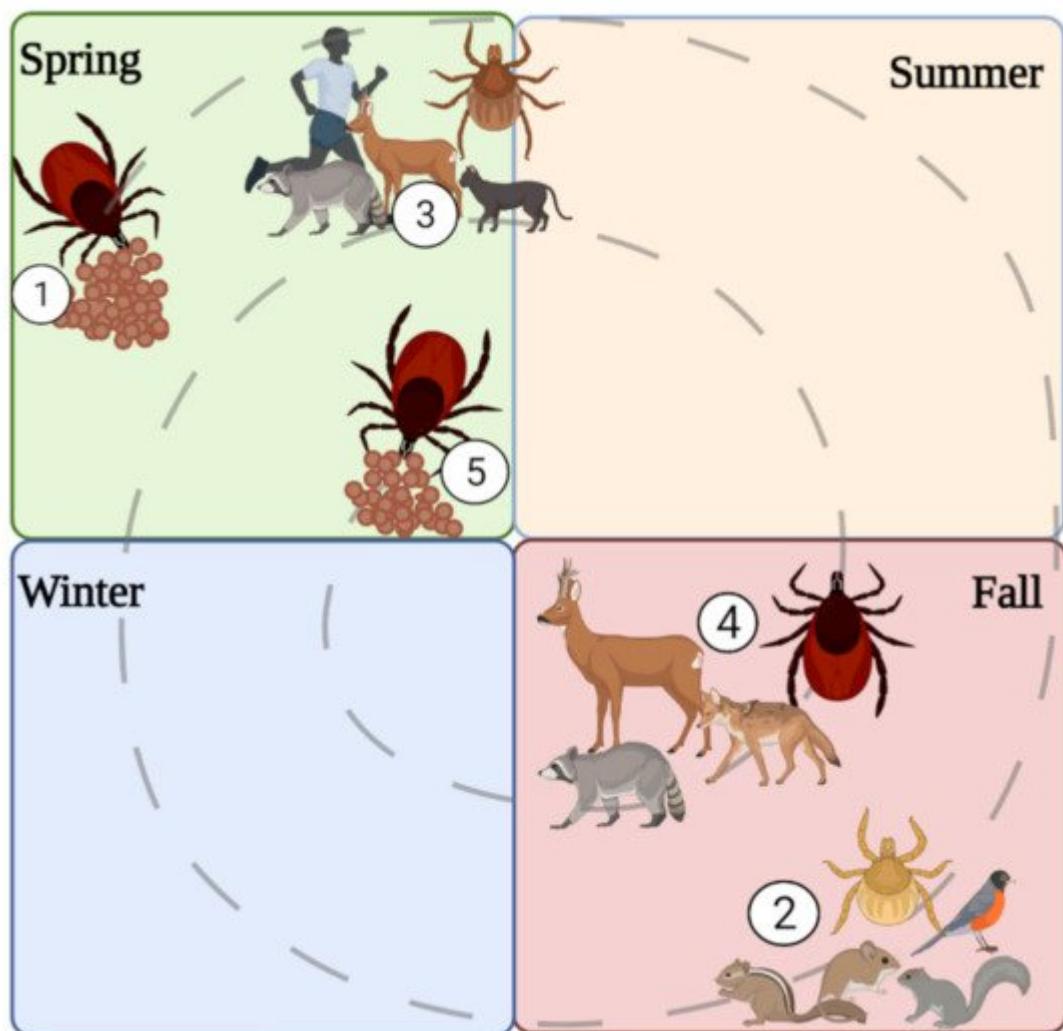


Figure 4. Life cycle of *I. scapularis*. (1) Female tick lays eggs in the spring. (2) The larvae hatch in the fall and feed on small mammals and birds. (3) The larvae overwinter and molt into nymphs. The nymph's quest on medium to large mammals. (4) The nymphs molt into adults, and the adults quest on large mammals. (5) The adults overwinter, and the females lay eggs in spring and then die. Illustrations were created using Biorender (biorender.com, accessed on 30 September 2021).

Ixodid ticks spend most of their life exposed to the environment, and thus, their survival depends on optimal ecological conditions. Suitable vegetation is necessary for tick survival, and vegetation is impacted by soil type which influences water drainage efficiency.

Meteorological variables, like temperature, humidity, and rainfall, affect moisture content in microhabitats, influencing tick reproduction rate, desiccation status, and host food availability.

5. Strain Variation and Stability

Multiple POWV strains exist in nature, but what causes certain strains to present in specific foci remains speculative. It has become evident that POWV is highly focal and stable [39]. In Connecticut, two distinct subclades were found only 40 km apart [40]. Likewise, a 5 km² TBEV focus in Germany revealed two circulating clades of virus that occupied different habitats (forest-meadow ecotone or forest). Over a decade, one clade showed more annual stability while the other appeared more sporadically. Moreover, nymphal counts varied annually. However, the minimum infection rate remained stable [41]. Similarly, in a Wisconsin focus, the proportion of infected ticks remained the same, even though tick density increased over a decade [42]. It is possible that certain strains may be found in more exclusive habitats, possibly driven by specific host populations in those habitats or other ecological variables not yet examined. More research should be conducted to elucidate the ecological mechanisms sustaining specific POWV strains in nature.

6. Climate Change and Anthropogenic Influence

In the US, ecological and climate modeling has predicted a growing distribution of *I. cookei* northward into Canada and a decreasing presence southward in the US, while *I. scapularis* is predicted to expand northward and westward [36], exposing new areas to tick-borne pathogens. Similarly, the white-footed mouse is expected to also expand northward and colonize new areas as temperature rises and winter length shortens [43], and this northward movement may be supported by earlier oak flowering which is correlated to rising spring temperatures earlier in the year [44]. It is possible that this effect may support other rodent species and pathogen reservoirs. Also, with increasing temperatures and shorter winters, groundhogs may exhibit less time in hibernation and more time actively outside of burrows, reproducing [45]. However, whether this has an impact on *I. cookei* population density or POWV prevalence is unknown.

With decreasing forest patch sizes, we may expect to see increased densities of *I. scapularis* [46], though fragmentation effects on POWV are unknown since the virus presents focally. Moreover, its effect on *I. cookei* is

undetermined since the tick may effectively be sustained in burrows. Furthermore, without knowing the reservoir for DTV, we cannot be sure how habitat loss directly impacts DTV prevalence.

While humans are contributing to global climate change and habitat reduction, increasing tick-borne disease prevalence, there are a number of ways that people can physically reduce tick densities and personal tick-borne pathogen acquisition, including POWV. Personal preventative measures for reducing pathogen attainment include frequently checking for ticks when outdoors, staying in the center of maintained trails, wearing EPA-approved repellents, wearing light-colored clothing, and tucking one's pants into their socks [47]. Prevention methods at home include cultivating a tick-free yard space by reducing leaf litter on the ground, removing weeds and bramble that may attract small rodents, creating a mulch barrier between the woods and the yard, and allowing ample sunlight to dry out the yard (reducing moisture for ticks) by regularly mowing and landscaping properly [47]. Host-targeted acaricides also are available to treat rodents and deer through passive topical applications [47]. By reducing hosts, treating hosts for ticks, landscaping to reduce tick abundance, and practicing personal prevention methods, tick-borne pathogen spillover to humans can be reduced. However, these methods are on the individual level, and long-term solutions require global participation.

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