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Eastern Equine Encephalomyelitis in Michigan: Historical Review of Equine, Human, and Wildlife Involvement, Epidemiology, Vector Associations, and Factors Contributing to Endemicity

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Abstract

Eastern equine encephalomyelitis (EEE) is a mosquito-borne viral disease that is an emerging public health concern in the state of Michigan. Although Michigan has one of the highest incidence rates of EEE in the United States, much of the information known about cases in humans, equines, and other animals residing in Michigan is unpublished. This article summarizes such information and explores spatial trends in the historic distribution of EEE in Michigan. Outbreaks in Michigan have occurred over an 80-yr interval, involving only horses in 1942–1943 and 1973–1976, and then episodically from 1980 to 2020, and involving horses, humans, and wild and domestic animals. An estimated 1,036 equine cases (confirmed and suspected) and 36 confirmed human cases have occurred, including 10 in 2019 (6 deaths) and 4 in 2020 (2 deaths). Human cases ranged in age from 1 to 81 yr; 70% were male, and fatality rate of 34.3%. Equine and human cases occurred from July to October, peaked in August, and cluster in space in southwestern and southeastern lower Michigan. Cases occurred in glacial outwash and ice-contact landscapes in glacial interlobate zones. EEE virus (EEEV) was recovered from *Culiseta melanura*, *Coquillettidia perturbans*, five species of *Aedes*, and other mosquito species near horse and human case sites. Virus isolations or presence of neutralizing antibodies in several passerine species of birds suggest broad EEEV–bird associations. White-tailed deer and other wildlife were also affected. Geographic spread to northern areas of the state suggests expansion of this disease system into new and unsuspected foci.

Key words: eastern equine encephalomyelitis virus, Michigan, horse, human, bird

Eastern equine encephalomyelitis (EEE) is a geographically widespread, yet focal, mosquito-borne zoonotic arboviral disease that has been documented to affect horses, wildlife, and humans in the eastern United States since the 1930s (Giltner and Shahan 1933, Fothergill et al. 1938, Scott and Weaver 1989, Corrin et al. 2021). EEEV is transmitted primarily by the mosquito *Culiseta melanura* (Coquillet) (Diptera: Culicidae) amongst passerine birds, whereas *Aedes* spp. and *Coquillettidia* spp. mosquitoes may serve as bridge vectors responsible for the transmission of EEEV to mammals (Armstrong and Andreadis 2010, Corrin et al. 2021). The geographic distribution of EEE has been largely restricted to the eastern coastal states and provinces of the United States and southeastern Canada, proceeding

along the Atlantic and Gulf coast states from New Hampshire to Texas (Letson et al. 1993, Armstrong and Andreadis 2013). Inland (noncoastal or near-coastal) foci have been described in upstate New York, central Alabama, at a single wildlife refuge in central Ohio, northwest Wisconsin, and in lower Michigan (McLean et al. 1985; Nasci et al. 1993; Lindsey et al. 2018, 2020; Oliver et al. 2020).

In Michigan, reports of outbreaks of EEE in equine species were documented beginning in the early 1940s (Shahan and Giltner 1943, Brown 1947), and depart from the typical geographic pattern in states of the eastern seaboard of the United States (Letson et al. 1993). The first human case of EEE in Michigan was reported in 1980 (MMWR 1980, Davenport et al. 1982), and since that time, the status of EEE as a reportable disease has facilitated annual surveillance in humans (MMWR 1980, 1992; Lindsey et al. 2018, 2020), horses (MMWR 1993, 1995), and various wildlife species (MMWR 1995). However, much of the information on cases of EEE in Michigan is unpublished. There has not been a historical review of EEE in Michigan, despite the state having one of the highest total number of reported cases in the US and endemicity having been recognized since 1942 (Shahan and Giltner (1943). Shahan and Giltner (1943) and Brown (1947) reported on the occurrence of equine cases in southwestern lower Michigan. McLean et al. (1985) analyzed the involvement of mammals and birds in an epizootic from 1980. Ross and Kaneene (1995, 1996) reviewed the epizootiology of horse cases from an outbreak in the early 1990s and considered risk factors for disease in horses. Schmitt et al. (2007) reported on cases of EEE infection in white-tailed deer in southwestern lower Michigan in 2005. Human cases of EEE have been reported previously (MMWR 1980, 1992; Davenport et al. 1982; Deresiewicz et al. 1997; Lindsey et al. 2018), including a review of the outbreak in 2019 when 10 human cases in Michigan were reported (Lindsey et al. 2020). Case reports in various animal species (McLean et al. 1985; MMWR 1993, 1995; Williams et al. 2000; Andrews et al. 2018; Thompson et al. 2021) and risk analysis of equid and white-tailed deer outbreaks (Ross and Kaneene 1995, 1996; Schmitt et al. 2007; Downs et al. 2015) have been published previously. Additionally, there are at least two unpublished master's theses dealing with the topic of EEE in Michigan (Shaw 1976, Solis 2000), and an important but unpublished report of studies of mosquito and bird involvement conducted from 1980 to 1982 (Newson 1983). These publications collectively reveal that the classic endemic pattern of EEE in Michigan occurs in the southwestern and southeastern areas of the Lower Peninsula from July to October, with case numbers peaking in August. The purpose of this article is to present a comprehensive historical review of mosquito, animal, and human surveillance data and to conduct preliminary exploratory spatial analyses of the historic distribution of EEE in Michigan. Further studies to investigate influences of weather and other factors are needed.

Materials and Methods

Study Area

The state of Michigan is located in the Great Lakes region of the United States, between latitudes 42–47° N and longitudes 83–90° W, and has an area of 250,740 km^2. The state consists of an Upper Peninsula (30% of land area) and a Lower Peninsula (Dorr and Eschman 1996, Eichenlaub et al. 1990), with these land masses bounded by four of the five Great Lakes. Elevation ranges from <200 to >600 m above sea level (Dorr and Eschman 1996). Topography varies from flat to rolling terrain. The climate is northern temperate and continental, moderated by the large lakes of the region, and encompasses two Köppen-Geiger regimes, the warm humid continental, and hot humid continental climates (Beck et al. 2018). A plant and climate tension zone representing a transition in cold-adapted vegetation is present at approximately the 43° N longitude (Andersen 2005). The 2010 census estimated a human population of 9,883,640 living in 83 counties, with 21 urban areas (https://www.census.gov/geographies/reference-files/2010/geo/state-local-geo-guides-2010/michigan.html). Equid survey data were from USDA (2008, 2019).

Pathologic and Virologic Analyses of Domestic Animal Cases

Suspected and confirmed cases of infection and death in equids (mostly horses, but occasionally others such as donkeys) and other domesticated animals were identified from reports from veterinary practitioners to the Michigan Department of Agriculture and Rural Development (MDARD), and through review of clinical and laboratory records. Brain tissues from equids were examined at the Veterinary Diagnostic Laboratory (VDL) at Michigan State University (MSU) for histopathology and immunohistopathology (Williams et al. 2000, Schmitt et al. 2007, Andrews et al. 2018). Before and after 2003, histopathology was done on brain tissues if the specimen was suitable. Before 2003, histopathology was the only diagnostic procedure used. From 2003 to 2010, virus isolation and standard gel-based PCR targeting the genomic region for the viral capsid protein (Schmitt et al. 2007) were done to detect EEEV RNA in samples. After 2010, virus isolation was discontinued and standard gel-based PCRs were confirmed with a second PCR targeting portions of the E3 and E2 envelope glycoprotein genomic region. All diagnostic testing was done in real time, not retrospectively. In some cases, tissues were forwarded to the National Veterinary Diagnostic Laboratory in Ames, IA for virus detection and isolation, in which case results were reviewed. Cases were recorded by address of residence of owner, and relevant information sought (breed, gender, age, travel history, date of onset, case outcome, vaccination history). The rates of EEEV vaccination of horses in Michigan are unknown. Similarly, domestic and zoo animals suspected of EEEV infection were examined (tissues or whole animals) for evidence of infection using the above methods. Historical data of the 1942–1943 and 1973–1975 episodes of equine encephalitis were taken from the literature and from archived records as samples were unavailable.

Human Cases

Human cases of EEE are required by Michigan public health law to be reported by physicians and laboratories to local (county/district) health departments and to the Michigan Department of Health and Human Services (MDHHS). Case reports were reviewed by public health staff with reporting physicians, reporting local health departments, and sometimes patients themselves. Specimens of serum or cerebral spinal fluid were obtained at the clinic and processed by IgM capture ELISA (Martin et al. 2000). Some specimens were forwarded to the Division of Vector Borne Infectious Diseases, Centers for Disease Control and Prevention (CDC), Fort Collins, Colorado, for serologic analysis and results returned to the MDHHS. Data of age, sex, travel history, diagnosis, illness onset date, course of illness, residence of patient, likely location of exposure to infected mosquitoes, and clinical outcome were recorded.

Wildlife Cases

Wildlife (birds and mammals) observed to be morbid, behaving with abnormal neurologic signs before death, found dead with no obvious cause of death, or unhealthy at time of hunter harvest were reported

to district staff of the Michigan Department of Natural Resources (MDNR). MDNR field staff or law enforcement personnel euthanized the animal if it was still alive, then froze and maintained the carcass frozen until it was transported to the MDNR Wildlife Disease Lab (WDL) for autopsy and specimen collection. Testing for the presence of EEEV was conducted by MSU VDL as described above for domestic animal cases. Data of the date the animal was collected, location to the township and a history of the animal were recorded.

Wild Birds

During the EEE outbreak in 1980, an investigation team from the CDC captured wild birds by mist net and sampled them by jugular vein blood for purposes of virus isolation and antibody detection. Domestic and penned birds were likewise sampled and tested. Methods and results were reported in McLean et al. (1985). In 1981 and 1982, similar unpublished studies at equine case sites in southern Michigan were conducted following methods in McLean et al. (1985). In 1981, bird mist net collections began on 2 June and continued to 16 September. Mist net collections were made at 26 locations in Kalamazoo, St. Joseph, Washtenaw, Ingham, Jackson, Oakland, and Livingston counties in 1981, with 2–4 visits per site. In 1982, 10 sites were visited with 2–4 visits per site. In addition, European house sparrows were collected by trapping at equine case sites, bled, and sera tested for antibodies to EEEV. As with mosquito collections described below, bird mist net collections were made primarily in locations where horse cases had been detected in 1980 and 1981. Serologic analysis for detection of neutralizing antibodies (1:20 and higher considered positive) and methods for virus isolation and identification were as in McLean et al. (1985). Critical data on wild bird studies were obtained from an unpublished report (Newson 1983).

Mosquitoes

Beginning in 1980, an investigative team from the CDC joined with officials from the Michigan Department of Health and Human Services and Michigan State University to conduct an unpublished study of mosquito populations in EEE-affected areas. Mosquito trapping and processing for virus isolation took place in 1980 (August–September), 1981 (June–September), and 1982 (June–September). Mosquitoes were collected at night with dry-ice baited CDC live traps, sorted to species, and processed for virus isolation following the methods described in Mitchell et al. (1996). Virus isolates were identified as described in McLean et al. (1985). Relevant data on these mosquito studies were obtained from an unpublished report (Newson 1983). In 1991, mosquitoes were trapped with dry-ice baited CDC light traps at four sites in eastern Jackson County, including at the index horse case site of that year and at three nearby locations, twice per week from the third week of August until the first week of September. Mosquitoes were treated as above for EEEV isolation.

Spatial Analyses and Landform Associations

Spatial analysis of historical EEE cases in Michigan involved calculating the average nearest neighbor index (ANNI) between each pair of the documented suspect and confirmed equid and human cases. Calculation of ANNI enabled detection of spatial clustering of cases throughout the state (Jacquez et al. 2005). A Wilcoxon signed-rank test (Zar 1984) was used to test for differences in average nearest neighbor distances for equid and human cases occurring before and after the approximate average midpoint across all years (MMWR week 34) for cumulative equid and human cases from 1980 to 2020 (Figs. 3C and 4B). Because we observed that many of Michigan's EEE cases occurred in areas with a history of glacial recession, we tested the associations of case locations with glacial landscapes and landforms. Vector digital data of glacial land systems for Michigan were from Lusch (2006), and accessed (January 2021) using ArcGIS Online (https://www.esri.com/en-us/arcgis/products/arcgis-online; Redlands, CA). To analyze associations between locations of equid and human cases with glacial features and landforms, a point-in-polygon analysis was done (Getis and Franklin 1987, Gatrell et al. 1996).

Results

History of Equid Cases and Associated Outbreaks

Review of reliable records of cases reported to state and federal authorities, in literature, or reliable diagnostic laboratory reports since 1942 (Fig. 1), found a total of 1,036 confirmed or suspect equid cases of EEEV in Michigan since the 1940s. The earliest known outbreak of EEE in Michigan occurred in 1942 (102 cases in four counties of southwestern Michigan) and 1943 (367 cases in 7 counties), all in the southwestern Lower Peninsula (Fig. 2A). EEEV was isolated from tissues of dead horses and birds during this period, representing the first records of EEEV in the state (Shahan and Giltner 1943, Brown 1947, Beadle 1952). The second reported isolation of EEEV from tissues of a dead horse from Michigan was in 1971 for which no case records were available (Maness and Calisher 1981). The next outbreak after the 1942–1943 episode occurred from 1973 to 1976, involving 44 horse cases, 36 of which occurred in 1973, four in 1974, three in 1975, and one in 1976. The first 10 of these cases were in southeastern Lower Peninsula (Fig. 2B), far from the epicenter of the 1942–1943 outbreak. Eventually, the outbreak became widespread in the Lower Peninsula. No publications documented it in detail, although an entomological investigation consisting of a mosquito survey with no virus analysis, was produced during this time (Shaw 1976). There are few other data from that episode, so details are scant but reports were reliable and perhaps conservative in terms of case numbers. Following these first two episodes, a series of outbreaks occurred from 1980 to 2020 (Figs. 1 and 3), with concentrations of equid cases in southwestern and southeastern lower Michigan (Fig. 3A) occurring in succeeding decades in contiguous multiyear episodes (Fig. 3B), and with most cases occurring in July, August, and September (Fig. 3C). Diagnostic capacity improved with the development of immunohistochemistry techniques available at the Veterinary Diagnostic Laboratory at Michigan State University in the 1990s, and suspect clinical equine cases could be more easily confirmed. The third outbreak from 1980 to 1984 involved 96 equid cases in 1980 (during which time the first human case of EEE was recorded, see below), 54 in 1981, nine each in 1982 and 1983, and one in 1984. McLean et al. (1985) isolated EEEV from the blood of several pheasants from flocks kept on farms near horse case sites in 1980. After a 4-yr hiatus of the detected activity, there was a single horse case in 1989 and an outbreak on a commercial game farm involving caged pheasants; both incidents were in southwestern lower Michigan (Letson et al. 1993, records of MSU VDL and MDARD, Williams et al. 2000). Anecdotes suggest many outbreaks in captive ring-necked pheasants raised for hunting purposes occurred during the 4-yr hiatus of detected activity. A fourth multiyear episode commenced in 1991–1996, followed by a hiatus with relatively low numbers of equid cases in 2000–2009. The

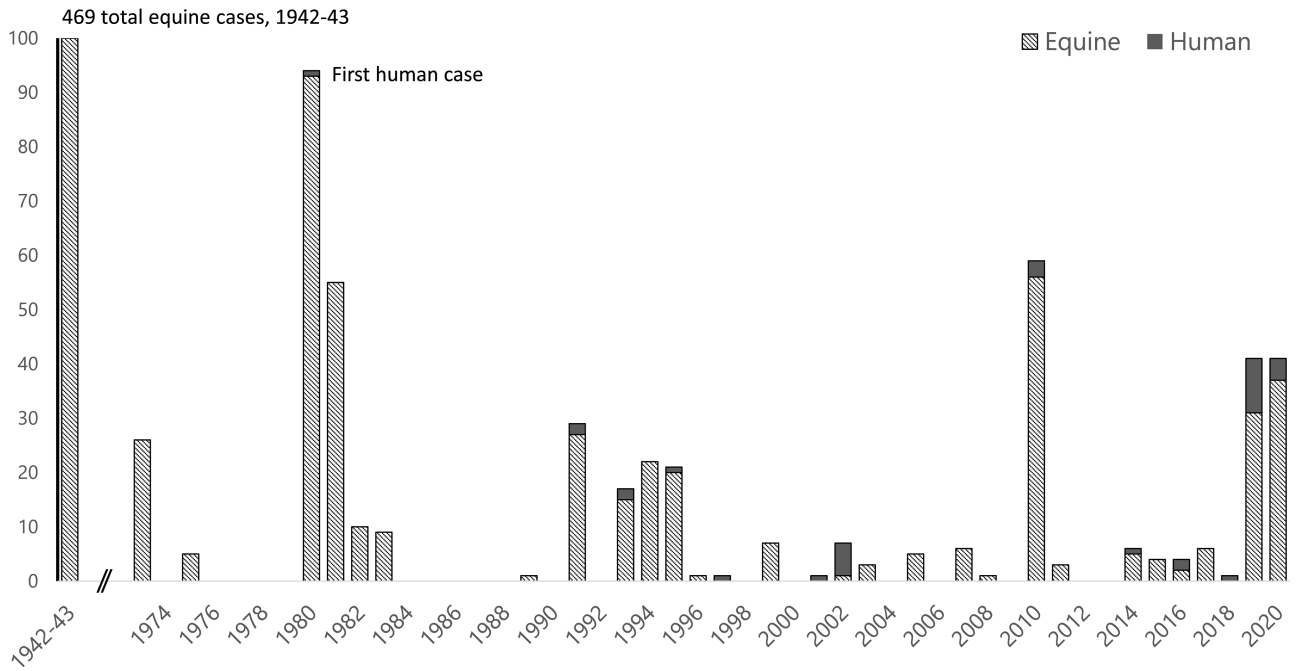

Fig. 1. Historical occurrence of reported (suspected and confirmed) equid and human (confirmed) cases of eastern equine encephalomyelitis in Michigan, 1942–2020.

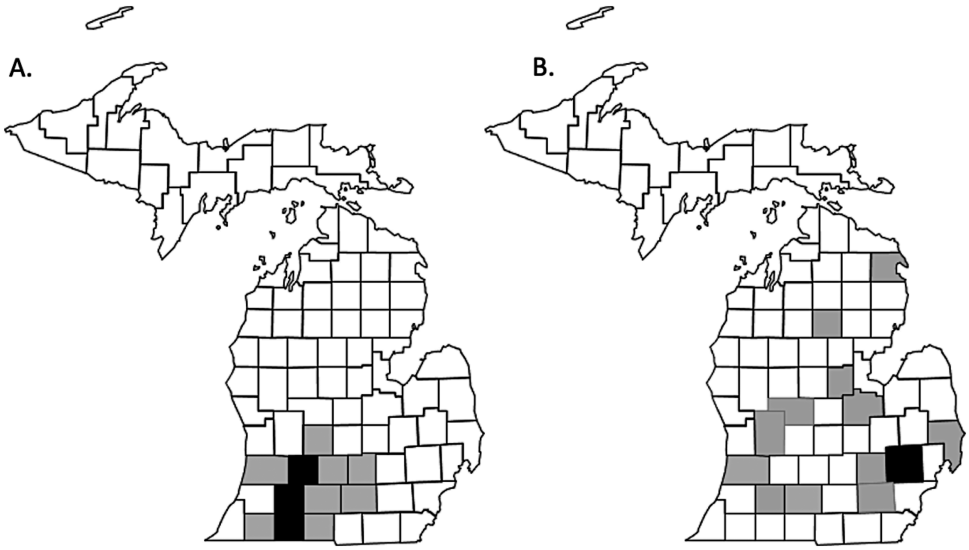

Fig. 2. Geographic distribution of equid cases of eastern equine encephalomyelitis in Michigan by county of residence. Darker counties, location of index equid cases, and of primary outbreak with temporally early cases. Lighter counties, fewer cases. (A) 1942–1943. (B) 1973–1976.

following decade was marked by nearly continuous annual activity with an increase in the frequency of human cases, starting in 2010 (134 equid cases, 3 human cases) and continuing in 2014 and 2018 (one human case each in 2014 and 2018, 4 equid and 2 emu cases in 2014, and 2 white-tailed deer cases in 2018), 2016 (3 human cases with 4 equid and 1 white-tailed deer cases), 2019 (31 equid cases, 10 human cases), and 2020 (37 equid cases, 4 human cases; Fig. 3A). The outbreaks in 2019 and 2020 are discussed in more detail below. Of 531 total horse cases from 1980 to 2020 for which outcome data were available, only 8 (diagnosed by serology) survived (1.5%). Of 145 equid cases from 2008 to 2020 for which sufficient information was available, 17 (11.7%) were reported as currently vaccinated against EEE virus (either by a veterinarian or owner), 110 (75.7%) had not been vaccinated, 11 (7.6%) were reported as having an expired vaccination, and 7 (4.8%) had unknown vaccination history.

Human Cases

A total of 36 human cases of EEEV infection with clinical disease were reported from 1980 to 2020 in Michigan (Table 1, Figs. 1 and 4). Although there were at least two outbreaks in horses in 1942–1943 and 1973–1976, no human cases were reported during those intervals, nor in between them. The first known human case in Michigan was in 1980 in a 13-yr-old male who suffered severe neurologic

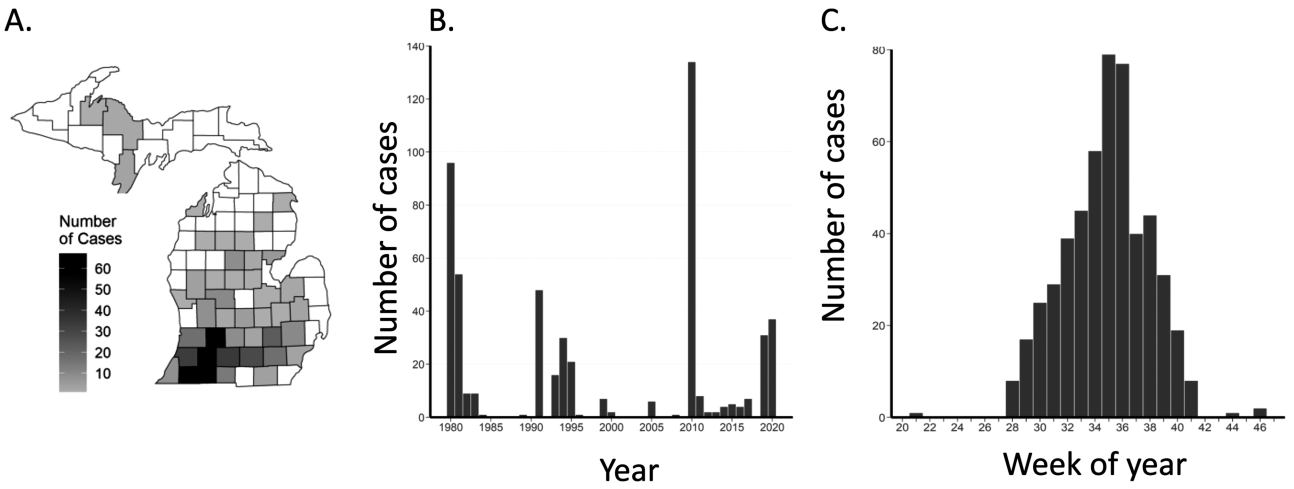

Fig. 3. (A) Geographic distribution of reported and suspected cases of eastern equine encephalomyelitis in equids, by county of residence (predominantly horses), Michigan, 1980–2020. (B) Number of reported and suspected cases of eastern equine encephalomyelitis in equids, 1980–2020. (C) Temporal distribution of reported and suspected cases of eastern equine encephalomyelitis in equids, by week of onset of disease, aggregated for 1980–2020.

Table 1. List of confirmed human cases of eastern equine encephalomyelitis with exposure in Michigan, 1980–2020

Case no.	Age (yr)	Sex	Onset date	County/jurisdiction[a]	Fatal (Y/N/unknown)
1	13	M	28 Aug. 1980	St. Joseph	Y
2	33	F	18 Aug. 1991	Jackson	N
3	62	F	19 Sept. 1991	Kalamazoo	N
4	73	M	2 Sept. 1993	Van Buren	N
5	UNK	M	1993	Barry	Unknown
6[b]	1	M	3 Sept. 1995	Cass	Y
7	25	M	8 Aug. 1997	Saginaw	Y
8	14	M	5 Sept. 2001	Livingston	Y
9	23	F	1 June 2002	Macomb	N
10	36	M	24 Sept. 2002	Macomb	N
11	39	M	17 Sept. 2002	City of Detroit	N
12	54	F	13 Sept. 2002	City of Detroit	N
13	77	M	21 Aug. 2002	Oakland	N
14	77	M	1 Sept. 2002	Ottawa	N
15	41	M	3 Aug. 2010	Kalamazoo	N
16	52	F	25 July 2010	Barry	N
17	61	M	12 July 2010	Kalamazoo	N
18	60	F	19 Sept. 2014	Van Buren	N
19	69	M	1 Oct. 2016	Marquette	N
20[b]	75	M	5 Aug. 2016	Marquette	N
21	75	F	10 Sept. 2016	Monroe	N
22	58	M	26 Aug. 2018	Allegan	Y
23	14	F	11 Aug. 2019	Kalamazoo	N
24	54	M	18 Aug. 2019	Berrien	Y
25	57	M	15 Aug. 2019	Berrien	N
26	63	M	27 Aug. 2019	Cass	Y
27	63	M	29 Aug. 2019	Barry	N
28	64	M	9 Aug. 2019	Kalamazoo	Y
29	68	M	12 Aug. 2019	Kalamazoo	N
30	72	M	21 Aug. 2019	Van Buren	Y
31	72	M	20 Sept. 2019	Cass	Y
32	78	M	25 Aug. 2019	Calhoun	Y
33	58	M	26 Aug. 2020	Barry	N
34	62	F	9 Sept. 2020	Montcalm	Y
35	81	M	18 Oct. 2020	Delta	N
36	7	M	14 Aug. 2020	Livingston	Y

[a]County of exposure when known, county of residence when exposure location is unknown.
[b]Out of state resident, but travel history indicates exposure in Michigan.

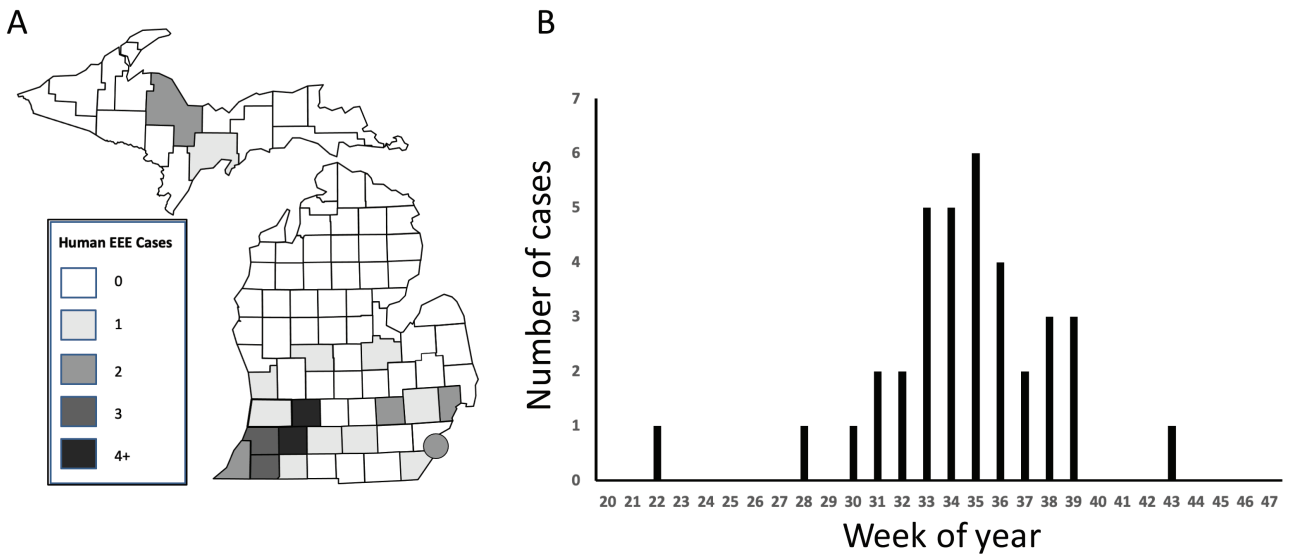

Fig. 4. (A) Geographic distribution of human cases of eastern equine encephalomyelitis by county of residence, Michigan, 1980–2020 (n = 35). City of Detroit shown as a circle. (B) Estimated week of onset of illness of human cases of eastern equine encephalomyelitis in Michigan, 1980–2020.

sequelae and died 14 mo following onset (MMWR 1980, Davenport et al. 1982). In response, the State of Michigan conducted an aerial spraying program of malathion in September to reduce risk of transmission to humans (Kaufman and Foote 1982). Of the 36 cases, excluding one for which details are unavailable, ages ranged from 1 to 81 yr, with a median of 61 yr, and 13 fatalities (36.1%; Table 1). Twenty-six (72.2%) of the cases were males. Most cases occurred in southwestern lower Michigan, but there were cases in Michigan outside of this region (Fig. 4A). Date of onset of illness ranged from June 1 through October 18, with the majority of illnesses occurring in August and September (Fig. 4B). Most patients had a clinical presentation consistent with encephalitis, and with the clinical diagnosis of meningitis or encephalitis. An exception to this pattern occurred in 2002, when 6 cases of EEE were discovered because of active surveillance, accompanied by serologic testing, during the epidemic of human West Nile virus (WNV) in humans in Michigan that same year. None of these cases were fatal and all reported a less severe clinical course, including meningitis assigned clinically. Recovery among survivors of the 36 cases was variable, with some recovering fully and others left with severe disabling neurologic sequelae. Two of the 36 cases occurred in residents of other states but who had spent time in Michigan where there was EEE activity in the days immediately before onset of their illness. These included a fatal case in a 1-yr-old infant from northern Indiana who spent considerable time in southwestern Michigan before illness onset. In 1991, a young woman in her third trimester of pregnancy with no history of out-of-state travel developed EEE viral encephalitis (Deresiewicz et al. 1997). Despite severe neuropathology, she survived and delivered a healthy infant at term.

Michigan experienced an intense outbreak of EEE that spanned summer and fall of 2019–2020 and resulted in the highest number of human EEE cases (14) and deaths (eight, 57.1%) in the state's history. The first year of the outbreak (2019) resulted in 10 human cases (6 deaths) and 50 animal cases in 20 counties, with an epicenter in the southern half of the Lower Peninsula (Fig. 5A). Human cases were confined to southwest Michigan in 2019; most locations of animal case were also in this region, but there were some cases in more northern counties of both the Upper and Lower peninsulas (Fig. 5A). The 2019 EEE outbreak and impact on human and animal health prompted state public health officials to undertake a multi-county aerial treatment campaign to kill adult mosquitoes, this being the first time of such an action since 1980. Treatments took place from September 28–October 10 and covered over 550,000 acres in 14 counties in the Lower Peninsula. In 2020, the epicenter of EEE activity unexpectedly shifted northward (Fig. 5B) and included four human cases (two deaths) with more widespread geographic and temporal distribution than in 2019, and 40 cases in animals, with equid onset dates earlier than in 2019. The episode of 2020 also unexpectedly encompassed more counties of the Upper Peninsula, including a human case in Delta County occurring late, in mid-October. This episode prompted a second consecutive year of aerial treatments between September 16–24 which covered 460,00 acres in 17 counties in the Lower Peninsula. Data on treatment efficacy and changes in mosquito populations after treatment are unavailable for both years. However, there were no additional cases identified within treated areas following treatment.

Wildlife

A total of 35 free-ranging white-tailed deer and five wild birds have been found infected with EEEV via capture IgM, immunohistochemistry techniques, and/or PCR in specimens collected by the Michigan Department of Natural Resources, Wildlife Disease Laboratory and submitted to the VDL at MSU (Fig. 6A). The earliest date of collection for a wild animal with EEE was July 27 (in 2019) and the latest date collected was November 4 (in 2009) with most animals being collected from mid-August to early October (Fig. 6B). The first outbreak in white-tailed deer occurred in southwest Michigan in 2005 (Schmitt et al. 2007); EEEV infection and clinical disease have been detected periodically in deer since then. In 2019, the largest outbreak of EEE in white-tailed deer occurred with 14 deer positive for EEEV from the southern Lower Peninsula, in the same region where equid and human cases occurred. Of the 35 EEE-positive deer, 31 were observed behaving abnormally (lacking fear of humans, wandering in circles, unable to walk or stand); 24 were euthanized by local authorities and seven were later found dead. In 2019, EEEV was detected by two-tier PCR in one mute swan from the southwestern Lower Peninsula, and one bald eagle and three ruffed grouse from the western Upper Peninsula (Fig. 6A). The mute swan was stumbling, then unable to move, and died. The bald eagle

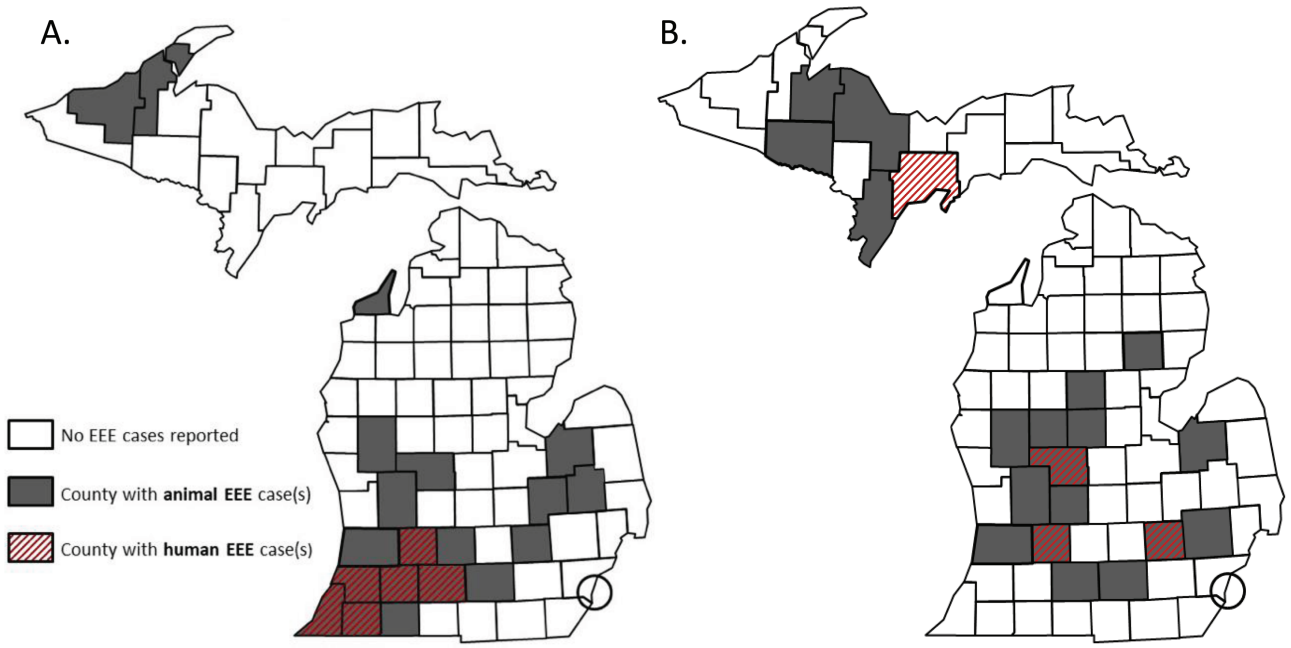

Fig. 5. (A) Distribution of human and animal (equid, deer, other) cases of EEE in Michigan by county, 2019. (B) Distribution of human and animal (equid, deer, other) cases of EEE in Michigan by county, 2020.

exhibited weakness and tremors and was euthanized by a wildlife rehabilitator after failing to improve with supportive care. Two of the ruffed grouse were hunter-harvested and observed to be thin at harvest. The third ruffed grouse was left at an MDNR field office with no history.

Wild Birds

Summaries of serologic analyses and virus isolation from wild birds mist-netted in 1981 and 1982 are shown in Supp Table 1 (online only). There was a total of 422 birds of 49 species sampled (1981: 296 birds of 32 species, 282 tested for antibodies and EEEV isolation; 1982, 127 birds of 26 species, 108 tested for antibodies and EEEV isolation). Eighty-four birds of 15 species had antibodies of 1:20 or greater, including 54 adults, 29 juveniles, and 1 of undetermined age. Among the species with relatively high seropositivity rates were blue jay, American robin, gray catbird, cardinal, eastern towhee, veery, indigo bunting, and wood thrush. The frequency distribution of antibodies is shown in Supp Fig. 1 (online only). Some antibody titers were high (1:640 or 1:1,280) including in juveniles (i.e., hatch year birds), suggestive of recent, local infection. EEEV was isolated from a juvenile yellow warbler taken near Spruce Lake, southern Ingham County, at the perimeter of the Waterloo State Recreation Area, on 18 August 1981; and a juvenile blue jay taken near Mohney Lake, western St. Joseph County, on 13 August 1981. A total of 1,788 house sparrows were collected in 13 counties in 1981 and 1,040 tested by the house sparrow trapping method; 2/96 (1.0%) from Calhoun County, and 4 of 133 (3.0%) from Kalamazoo County had antibodies to EEEV. The remainder were seronegative. In 1982, a total of 2,517 house sparrows were collected in 11 counties and 2,344 tested; one of 277 (0.4%) from Monroe County was positive for antibodies to EEEV, and the remainder negative.

Mosquitoes

From 1980 to 1982, a total of 381,643 female mosquitoes (Diptera: Culicidae) of 39 taxa were sampled, pooled into 8,055 pools, and tested for EEEV infection (Supp Table 2 [online only]). From these samples, a total of 90 EEEV isolates were recovered: 48 from *Cs. melanura* (5,310 in 320 pools; Minimum Infection Rate (MIR) of number infected per 1,000 tested = 9.04), 20 from *Coquillettidia perturbans* (Walker) (165,119 in 1,901 pools; MIR = 0.12), five from *Aedes vexans* (Meigen) (76,421 in 1,011 pools; MIR = 0.07), four from undetermined *Aedes* spp. (48,842 in 737 pools, MIR = 0.08), three from *Aedes canadensis* (Theobald) (15,183 in 387 pools; MIR = 0.20), three from *Culiseta minnesotae* Barr (563 in 96 pools, MIR = 5.33), two from *Culex* (*Culex*) spp. (3,245 in 254 pools, MIR = 0.62), and one each from *Aedes cinereus* Meigen (6,587 in 339 pools, MIR = 0.15), *Aedes triseriatus* (Say) (957 in 203 pools, MIR = 1.04), *Culex pipiens* Linn. (17,978 in 491 pools, MIR = 0.06), *Culex territans* Walker (102 in 69 pools, MIR = 9.80), and *Psorophora ciliata* (308 in 100 pools, MIR = 3.25). Of 4,372 mosquitoes of 13 taxa sampled in eastern Jackson County in 1991, sorted into 244 pools, and processed for virus isolation, there was a single isolate of EEEV from 645 *Cq. perturbans* in 41 pools (MIR = 1.6; Table 2).

Spatial Analyses and Landform Associations

Of 569 equid and human cases reported from 1980 to 2020, 545 (511 horses, 34 humans) had sufficient geographic information for spatial analyses. These cases showed a significant tendency to form clusters (Fig. 7A). The ANNI for equid and human cases combined was 0.378 ($P < 0.0001$, significantly below the neutral value of 1.0). In addition, the distance of each point to its nearest neighbor was tested to determine whether the average nearest neighbor distance was greater for the cases in weeks 35 and later compared to those in weeks 34 and before, using a one-tailed Wilcoxon rank test ($P = 0.0004$). Of 569 equid and human case records, 538 had sufficient information of address and date of onset (or report if onset unknown) for this analysis. There were 232 cases that occurred before and during MMWR week 34 and 306 that occurred during MMWR week 35 onwards. The significant result of the Wilcoxon rank test indicates that cases that occurred later had a significantly greater average distance to their nearest neighbor compared to

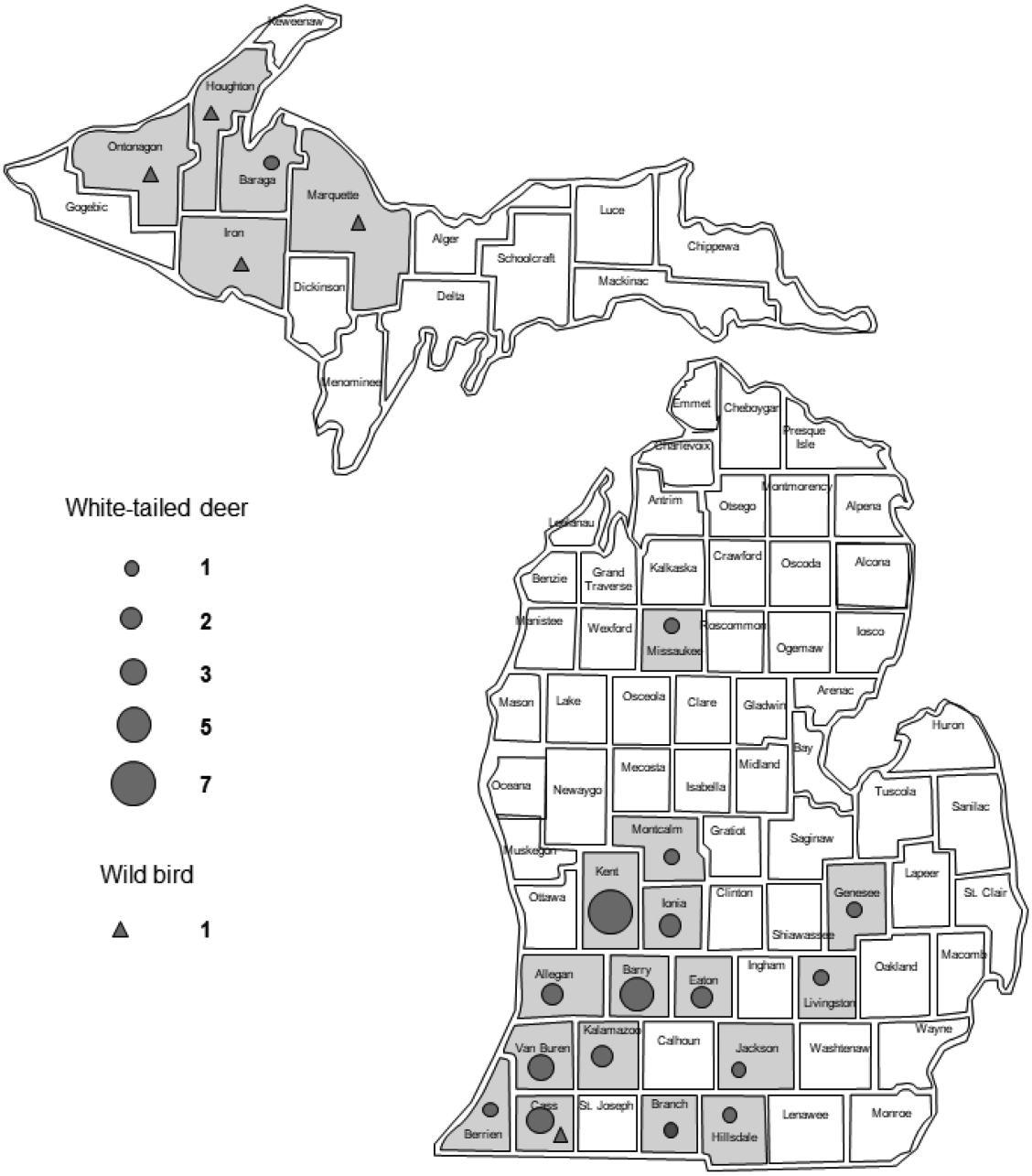

Fig. 6. (A) Map of Michigan showing location of sightings of wildlife confirmed with infection with eastern equine encephalomyelitis virus, 2005–2020. Symbols are white-tailed deer, ruffed grouse, and bald eagle. (B) Date of sightings of wildlife confirmed with infection with eastern equine encephalomyelitis virus, Michigan, 2005–2020.

earlier cases. Based on empirical observations of where clusters of cases were located, we postulated that equid and human cases predominantly occurred in areas with successional glacial moraines bounding glacial outwash and glacial ice-contact landforms, in particular the Battle Creek Interlobate and Jackson Interlobate regional landscape ecosystems of southwestern Michigan and southeastern Michigan, respectively (Fig. 7B). To test this hypothesis, horse and human cases were plotted by the address of residence over a quaternary geology map of Michigan showing polygons of glacial outwash, ice-contact outwash, and moraine features (Fig. 7A; Farrand and Bell 1982, Albert 1995, Lusch 2006), and a points-in-polygon analysis applied. Notably, 515 (94.5%) of the 545 cases occurred in three such quaternary glacial features when 378 were expected in a random distribution model for mainland Michigan (Fig. 7B), a highly significant spatial association with glacial landforms (Monte Carlo randomized distance test, $P = 0.005$).

Discussion

Our primary purpose here was to present a comprehensive, historical overview of EEE in Michigan. We emphasized empirical investigations and general conclusions, considering as many elements of this disease system and its manifestations as possible. We availed a considerable amount of unpublished information on mosquito vectors, wild birds serving as vertebrate hosts in the natural transmission cycle, and records of cases of disease in wildlife, domestic animals, and humans.

Table 2. Isolation of eastern equine encephalomyelitis virus from mosquitoes sampled in eastern Jackson County, Michigan near EEE horse cases, by dry ice baited CDC light trap, August–September, 1991

Species	Number tested	Pools tested	Number of EEE isolates	Minimum infection rate
Aedes cinereus	162	24	0	0
Ae. triseriatus	4	4	0	0
Ae. vexans	181	16	0	0
Aedes spp.	7	1	0	0
Anopheles punctipennis	149	24	0	0
An. quadrimaculatus	2,727	83	0	0
An. walkeri	9	3	0	0
Coquillettidia perturbans	645	41	1	1.5
Culex erraticus	210	25	0	0
Cx. pipiens	14	4	0	0
Cx. restuans	255	15	0	0
Cs. melanura	5	3	0	0
Uranotaenia sapphirina	4	1	0	0
Total	4,372	244	1	

The history of EEE in Michigan reveals a series of episodic outbreaks, each generally forming a multi-year episode, where one large outbreak year was followed by successive years of relatively less activity. Vaccination to protect horses against EEE has been available since at least the 1960s and may help reduce outbreak severity. However, many horses that died of EEE were never vaccinated. The cumulative number of human cases has increased since 1980 while the ratio of horse to human cases has decreased, perhaps because the horse population in Michigan has been declining. The estimated horse and pony population were 130,000 in 1996, 155,000 in 2007, 87,998 in 2012, and 64,200 in 2017, representing more than a 50% decline over a 20-yr period (USDA 2008, 2019). Since 2000, infection and disease in various animal species were probably more readily detected as funding for arbovirus surveillance became available following the emergence of WNV in the US.

The multi-year outbreak in 1980–1984 signaled the first documented human case of EEE in Michigan (MMWR 1980, Davenport et al. 1982); the first in-depth investigations of EEEV exposure in horses (Monath et al. 1981, McLean et al. 1985); isolations of EEEV from *Cs. melanura*, *Cq. perturbans*, and other mosquitoes (see Results, Supp Table 2 [online only]); isolation of EEEV or detection of antibodies to EEEV in wild and domestic birds (McLean et al. 1985; see Results, Supp Table 1 [online only]) from the same areas where horse cases resided; and an aerial application of malathion as an intervention (Kaufman and Foote 1982). These findings, taken together and notably near the residence of the first human case in Michigan in 1980, confirm relationships of EEEV to mosquito vectors and wild bird amplifying hosts, and connect EEEV to horse and human disease at a localized geographic scale. However, the mechanism of virus spread away from amplification areas to anthropogenic environments is unknown and needs further study.

In 1989, there was a widespread epizootic and epidemic of EEE in the eastern United States involving nearly all states bordering the Gulf of Mexico or the Atlantic Ocean (Letson et al. 1993). No other inland states reported cases, except for a single horse in Tennessee and the sole horse case and a pheasant epornitic in Michigan (Letson et al. 1993, Williams et al. 2000). 1991–2000 revealed nearly continuous EEEV activity amongst equids in all years but 1992, 1997, and 1998. During this period, the cumulative number of human cases increased, including a case in 1997 that was unaccompanied by animal cases and was outside of the classic EEE endemic zone in Michigan. During the period from 1991 to 2000 there was an increase in frequency of human EEE cases (Fig. 1). By contrast, 2000–2009 was a period of relative quiescence in EEE activity, with 6 equid cases in 2005 and 1 in 2008, and no reported human cases apart from 6 recognized in 2002. 2010–2019 was marked by continuous EEE activity in equids and a total of 22 human cases. Ten of the human cases occurred in 2019 and represented the highest number of human cases ever reported in 1 yr. Accompanying this demonstrable increase in EEE activity over time was an expansion in the geographic range of occurrence of equid, human, and wildlife cases. Similar expansions in geographic range for EEE have been observed in New York State and New England (Armstrong and Andreadis 2013; Oliver et al. 2016, 2020).

An outlier in the human case surveillance data was the detection of six human cases of EEE in 2002. These human EEE cases were detected during the significant national outbreak of WNV, which included Michigan (O'Leary et al. 2004), resulting in intensified active surveillance for human cases of arboviral disease. Cerebral spinal fluid and/or serum from suspect cases of meningitis and encephalitis were tested at the state public health laboratory for IgM antibodies against WNV, St. Louis encephalitis virus, California Group virus, and EEEV. Likely owing to this increase in active surveillance, 10 human cases of La Crosse encephalitis were also detected in 2002 in Michigan, far exceeding the typical number of reported cases of this disease per year in the state (MDHHS, unpublished data). Most of the human EEE cases in 2002 reported a relatively moderate illness and recovered, representing lesser severity than is typically seen in Michigan. Based on these observations, it is likely that many human EEE infections in Michigan could go undetected, particularly if the illness is minor or self-limiting. However, Letson et al. (1993) through an analysis of several EEE episodes suggest that the number of asymptomatic cases and the inapparent to apparent case ratio are quite low during outbreaks. These unusual cases in 2002 also occurred outside of the typical EEE risk areas of the state (such as the City of Detroit and nearby Macomb County), which remains unexplained. Active surveillance for EEE in Michigan may reveal a greater burden than previously suspected.

Our review of cases indicates that EEE is becoming an increasingly recognized public health problem and serious health concern for many animal species. For example, domestic dog puppies, and wolf puppies in a zoo in southwestern Michigan, succumbed to EEEV infection in Michigan recently (Andrews et al. 2018, Thompson et al. 2021). The first outbreak in Michigan wildlife occurred in 2005, involving 8 white-tailed deer, and since that time periodic cases in deer from 2009 to 2019. White-tailed deer

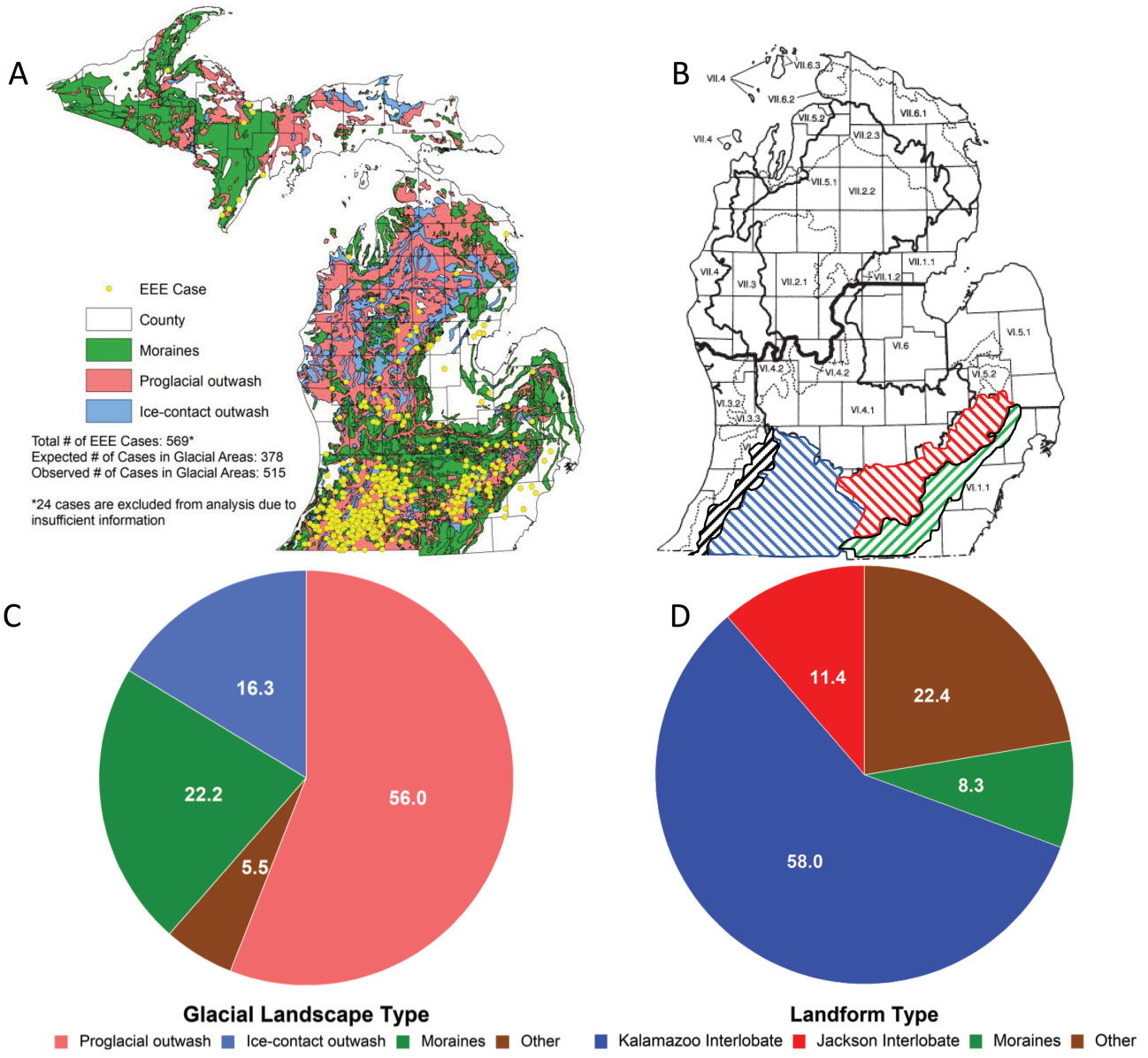

Fig. 7. (A) Distribution of equid cases of eastern equine encephalomyelitis in lower Michigan, 1980–1995, in relation to quaternary glaciated landscapes of glacial outwash and ice-contact outwash. (B) Kalamazoo Interlobate (blue) and Jackson Interlobate (red) glacial landforms in lower Michigan with adjacent, successional till moraine (black and green hash; redrawn from Albert 1995, Fig. 5, p. 22).

have also been reported infected with and apparently dying from EEEV in New York State (Oliver et al. 2016). Additionally, two emus (*Dromaius novaehollandiae*) from farms in Schoolcraft and Oakland Counties in 2009; and two emus from a farm in Ingham County in 2014; were confirmed to have died of EEE (MDARD and MSU VDL, unpublished case records). Antibodies to EEEV found in sera from waterfowl, pheasants, and wild turkeys in southwestern Michigan confirm exposure in birds (Brown 1947). Isolations of EEEV in Michigan by McLean et al. (1985) and detection of neutralizing antibodies reported here (Supp Table 1 [online only] and Supp Fig. 1 [online only]) demonstrate local infection in diverse passerine bird populations (both resident and seasonal). McLean et al. (1985) isolated EEEV from a weak and lethargic *Empidonax* flycatcher, and suggested that EEEV causes mortality in wild passerine birds. Passerine birds contribute significantly to the enzootic transmission of EEEV (Scott and Weaver 1989, Emord and Morris 1984, Crans et al. 1994, Garvin et al. 2004) and local enzootic transmission of EEEV amongst passerine birds and ring-necked pheasants has been demonstrated to occur within Michigan (Table 2; McLean et al. 1985). Additionally, EEEV was detected in ruffed grouse, a mute swan, and a bald eagle for the first time in the state in 2019–2020. Detection in ruffed grouse and a bald eagle in 2020 in the western Upper Peninsula suggests expanding geographical occurrence of EEE in wildlife and a greater diversity of affected species in the state. EEEV infections in ruffed grouse have also been reported in northern areas of Minnesota and Wisconsin contiguous to the area affected in the Upper Peninsula of Michigan (Anderson et al. 2021). The risk factors for ruffed grouse, a nonmigratory, upland bird species, are unknown, highlighting that poorly understood EEEV transmission processes may be occurring across a broad northern region. However, routine active surveillance for EEE in wild bird populations is lacking in Michigan. Seroprevalence studies may reveal local

virus transmission activity trends, improve knowledge of the true extent and burden of EEE in Michigan, and provide early warning of risk to residents via active animal surveillance.

Letson et al. (1993) suggested that the occurrence of horse cases could be used as a strong spatial predictor of local risk of human cases but could not be used as advance warning for human cases because of the coincidental timing of the epidemic curves of horse and human cases. Those observations are supported for Michigan (Figs. 3A, C and 4A, B). In Massachusetts, weekly changes in EEEV infection rates in *Cs. melanura* can be used to infer risk in humans. Low risk summers have lower EEEV infection rates that develop later as the summer progresses compared to high-risk summer transmission seasons (Hachiya et al. 2007). Observations such as these validate routine mosquito sampling for EEEV infection rates as a surveillance tool and coordinating vector control. Michigan's history of EEE outbreaks and trends in other states indicate that ecologic conditions for the virus are possibly changing, leading to sustained outbreaks from year to year that are more intense and widespread. This trend has large implications for the residents of Michigan, as comprehensive local vector surveillance and control programs are lacking in most of the areas where EEE activity has been found. However, no such programs have been implemented in Michigan despite the intensification of EEE infections in humans, horses, and wildlife over several decades, and even with decisions to implement aerial applications of insecticide to control vector populations in 1980, 2019, and 2020.

Mosquito surveillance for EEEV has occasionally occurred in Michigan but in reaction to outbreaks. Results of isolation of EEEV from mosquitoes during the 1980–1982 period and from 1991 reveal findings like those of other regions of the northeastern United States, such as New England, New Jersey, and New York State, that *Cs. melanura* is the enzootic and possibly epizootic vector of EEEV, and that other species such as *Cq. perturbans* and *Ae.* spp. may serve as bridge vectors (Grady et al. 1978, Howard et al. 1988, Andreadis et al. 1998, Oliver et al. 2018). In this study, the greatest number of viral isolates was from *Cs. melanura* and the MIR was highest in that species as well, while the second greatest number of viral isolates came from *Cq. perturbans*. Notably, three isolates came from *Cs. minnesotae;* it may serve as a secondary vector of EEEV as has been proposed for *Cs. morsitans* (Supp Table 1 [online only]). However, there is no evidence of the involvement of the latter species in EEEV transmission in Michigan, even though this species is present and widespread in the state (Cassani and Newson 1980, Darsie and Ward 2004) and has been implicated as an enzootic vector in western New York State (Oliver et al. 2018). Both *Cq. perturbans* and *Ae. canadensis* have been proposed as bridge vectors of EEEV elsewhere based on recovery of EEEV from field samples and vector competence characteristics (Crans and Schulze 1986, Andreadis et al. 1998, Armstrong and Andreadis 2010, Oliver et al. 2018); the recovery of EEEV here from these two species supports that possibility for Michigan. *Aedes sollicitans* occurs in focal populations in Michigan, particularly in areas with surface salt contamination (Cassani and Newson 1980, Copeland and Walker 1986), but it is unlikely to be a bridge vector in the state given its highly localized distribution, in contrast with New Jersey (Crans et al. 1986). However, Armstrong and Andreadis (2010), Molaei et al. (2015), and Oliver et al. (2018) have advocated that *Cs. melanura* solely may be responsible for EEEV transmission to mammals, including horses and humans, during epizootic outbreaks, given the tendency of this species to feed at low frequencies on mammals outside of swamps and for it to disperse long distances. In Michigan, there are few data on host selection tendencies of *Cs. melanura* and no information on dispersal, so its role as epizootic and epidemic vector is unknown. However, commonly in Michigan there are human residences and neighborhoods located closely to *Cs. melanura* habitat so the interface between this primary vector and humans is a consideration for the risk of human disease.

The mosquito species reported here are consistent with those historically found in Michigan (Cassani and Newson 1980), except that *Psorophora columbiae* (Supp Table 2 [online only]) was well out of range (Darsie and Ward 2004) but has been found in Saginaw County, Michigan, in certain years in breeding populations (E. Walker, unpublished). The few specimens of *Anopheles crucians*, also well out of typical geographic range, were confirmed (Taylor et al. 1984). The finding of *Cs. incidens* in Michigan is unusual and could represent a misidentification or a new state record (Supp Table 2 [online only]), whilst occurrence of *Cs. minnesotae* in the Lower Peninsula of Michigan extends the range of this species where previously it had been absent (Darsie and Ward 2004). Many *Cs. melanura* female specimens taken in Michigan have bands of pale scales along the basal abdominal segments, which can confound identification as dichotomous keys indicate that such bands are lacking (Darsie and Ward 2004). However, this nonheritable character is environmentally induced and present commonly in *Cs. melanura* populations (Andreadis and Munstermann 1997).

Our spatial analyses of association of equid and human EEE cases invoked terms and concepts derived from surficial (i.e., quaternary) geology (Farrand and Bell 1982), which is the analysis of landforms and materials accumulated over bedrock and associated with recent geologic processes, particularly glaciation (Dorr and Eschman 1996). Landform classifications and ecological landscapes (e.g., terrestrial and aquatic systems, plant communities) were from Albert (1995). Our analysis demonstrates a strong association of most human and horse cases of EEE with the Kalamazoo Interlobate (with Battle Creek Outwash Plain and Cassopolis Ice-Contact Ridges landforms) and the Jackson Interlobate (with the associated end moraines) landforms; these associations apparently favor endemicity of the EEE disease system, providing a regional means of risk assessment for horses, humans, and wildlife living in those areas (Fig. 7A–D). Hydrologic processes within these landforms resulted in the establishment of extensive flat to rolling terrain of small kettle lakes, wetlands, and drainage systems in geographic correspondence with the edges of the retreating glacial lobes, often within distinct tunnel valleys (Kehew et al. 1999, Fisher et al. 2005). The poorly drained outwash along ice-contact ridges and glacial outwash zones facilitated the formation of mixed-hardwood swamps, tamarack swamps, bogs, and fens as the kettle lakes went through a process of geomorphological transformation (such as ice block melting and land collapse into kettle lakes) and ecological succession from lakes to hardwood and conifer swamps and bogs. Nested within these systems can be found acidic bogs with *Sphagnum* moss intermixed with hardwood and conifer swamps, manifesting distinct wetland plant communities (Kost et al. 2007, Cohen and Kost 2008, Cohen et al. 2020). These wetland types with their characteristic plant communities (Comer et al. 1995) have hydrologic and physiographic features, originating from the specific glacial processes identified here, supporting the specialized larval habitat for *Cs. melanura*, therefore favoring production of adult *Cs. melanura* (Pierson and Morris 1982, Andreadis et al. 2012). Larvae of *Cs. melanura* occur in water-filled cavities in sphagnum mats formed around roots of tamarack trees or shrubs set into the bog mat (Garvin et al. 2004). These wetland plant communities in Michigan to a certain extent represent a departure from the swamps characterized by Atlantic white cedar (*Thuja occidentalis*), red maple, yellow birch (*Betula alleghaniensis*), and eastern hemlock (*Tsuga canadensis*) trees associated with *Cs.*

melanura swamp habitat in the northeastern United States (Morris et al. 1980, Skaff et al. 2017), particularly with tamarack and not Atlantic white cedar or eastern hemlock as the indicator tree species. We propose that the sphagnum bog wetlands and associated tamarack-dominated swamps and red maple swamps serve as enzootic foci for EEEV Michigan, like at the single, small focus in Ohio (Killbuck Marsh Wildlife Area), where a sphagnum bog (Brown's Lake Bog) produces *Cs. melanura* (Nasci et al. 1993, Garvin et al. 2004). These associations, which require further research for purposes of verification, have some similarity to the mixed-hardwood swamps described by Morris et al. (1980) in the EEE endemic area of Oswego County and nearby counties of upstate New York where distribution of *Cs. melanura* larvae has been described (Pierson and Morris 1982), and to that of a recently described, new EEE focus in Rutland County and Addison County, Vermont (Molaei et al. 2015), but without the presence of tamarack trees or sphagnum bogs. Nonetheless, similar glacial processes may have resulted in the geographic distribution of the kinds of mixed hardwood and conifer swamps associated with EEE foci in the northeastern United States and in New York State (Morris et al. 1980, Howard et al. 1996, Molaei et al. 2015, Skaff et al. 2017). As EEEV expands its range in the northern tier of its presently known distribution (Armstrong and Andreadis 2013; Oliver et al. 2016, 2018, 2020) and becomes increasingly recognized as an emergent disease (Morens et al. 2019), investigations of landforms that may provide biological elements receptive for *Cs. melanura* ecology and EEEV foci to develop need to be done, and changes in temperature regime favoring a longer growing season as well. These specific landforms with the observed clusters of equid and human cases add specificity and sensitivity to such predictions, beyond the more generalized wetland associations as proximal risk factors for EEE for equids and humans, such as the incomplete drainage lake type (Davis 1931, Ross and Kaneene 1995), or swamps and wetlands (Schmitt et al. 2007, Downs et al. 2015).

Some animal and human cases occurred in areas not associated with high-risk zones for EEE in Michigan identified above (Fig. 7A and B). Some of these cases are likely due to epidemic spread from endemic sites. Solis (2000) examined the spatiotemporal pattern of horse cases in southwestern Michigan during the 1980–1983 episodes and showed clusters of horse cases early in the outbreaks of each year, followed by horse cases farther from these early nidi of cases later in the season. These findings are corroborated by our analysis of nearest neighbor distances of cases, which were smaller up to MMWR week 34 and farther afterward, suggesting spread of the virus from early enzootic foci to outside of them and/or amplification in sites that vary in their initial enzootic transmission intensity so that some sites reach levels of detectability sooner than others. Future spatiotemporal analyses may include division of the transmission period into more than two segments to reveal nearest-neighbor distances changing over time and other trends in EEE activity in Michigan.

This paper summarizes over 80 yr of reports of EEE illness and studies in people, mosquitoes, wildlife, domesticated animals in Michigan. It describes patterns of occurrence that have been observed for decades along with evidence of geographic expansion and potential association to postglacial landforms throughout the state. Furthermore, this paper emphasizes that EEE is an emerging arbovirus disease in Michigan for which there is currently no sustained, public funding for surveillance and response. Further studies into the mosquito, host, and abiotic factors of the disease cycle are needed to further characterize the ecology of EEE in Michigan and the Upper Midwest with a goal to predict disease occurrence in the region.

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