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Comorbid conditions as risk factors for West Nile neuroinvasive disease in Ontario, Canada: a population-based cohort study

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Abstract

West Nile neuroinvasive disease (WNND) is a severe neurological illness that can result from West Nile virus (WNV) infection, with long-term disability and death being common outcomes. Although WNV arrived in North America over two decades ago, risk factors for WNND are still being explored. The objective of this study was to identify WNND comorbid risk factors in the Ontario population using a retrospective, population-based cohort design. Incident WNV infections from laboratory records between 1 January 2002 – 31 December 2012 were individually-linked to health administrative databases to ascertain WNND outcomes and comorbid risk factors. WNND incidence was compared among individuals with and without comorbidities using risk ratios (RR) calculated with log binomial regression.

Three hundred and forty-five individuals developed WNND (18.3%) out of 1884 WNV infections. West Nile encephalitis was driving most associations with comorbidities. Immunocompromised (aRR 2.61 [95% CI 1.23–4.53]) and male sex (aRR 1.32 [95% CI 1.00–1.76]) were risk factors for encephalitis, in addition to age, for which each 1-year increase was associated with a 2% (aRR 1.02 [95% CI 1.02–1.03]) relative increase in risk. Our results suggest that individuals living with comorbidities are at higher risk for WNND, in particular encephalitis, following WNV infection.

Introduction

West Nile neuroinvasive disease (WNND) is a severe neurological illness that develops in less than 1.0% of individuals infected with West Nile virus (WNV) [1]. WNND manifests predominantly as encephalitis (WNE), meningitis (WNM), or acute flaccid paralysis (WNP), resulting from virus entry into the central nervous system and inflammation of the brain parenchyma, or meninges, or disruption of specialised spinal cord cells, respectively [2]. WNND can lead to severe outcomes like death, coma, and persistent, debilitating sequelae (e.g. neuromuscular paralysis) with many individuals requiring extended hospitalisation and post-illness rehabilitation [3–7]. Antiviral medication specific to WNV has not been developed, so supportive care and pain management are the only treatment options available for individuals with WNND, and the care is expensive. Estimated attributable 10-day costs for acute WNND were $3576 in 2014 Canadian dollars, three times higher than for acute WNV [8].

Although WNV was first detected in North America over two decades ago, no Canadian studies have examined pre-existing comorbid conditions as risk factors for developing WNND. A number of studies from the United States (and one from Greece) have identified older age [9–14] and male sex [11–13] as risk factors for WNND, along with chronic diseases like diabetes [10, 14–17] and hypertension [10, 14–17]. Other comorbidities such as cancer [10, 14–17], cardiovascular disease [3, 10, 14, 15, 17], and kidney disease [10, 14–17] have also been suggested as risk factors.

In Ontario, Canada's largest and most populous province (and one of the provinces most-affected by WNV), future demographic and environmental changes are likely to increase the number and incidence of infection and WNND. As the population ages, more individuals will be at higher risk of developing WNND, while as the climate warms, extending the WNV vector breeding season and expanding the geographic range of WNV transmission, more Ontarians may be exposed to WNV [18–20]. WNV is a notifiable disease in Ontario, and the province has recorded laboratory-confirmed WNV infections since 2002. By linking laboratory data with province-wide health administrative databases, this study aimed to

identify comorbid risk factors for WNND in the Ontario population among individuals with incident WNV infection between 2002 and 2012.

Methods

Study design

We conducted a retrospective population-based cohort study to estimate the risk of WNND following infection with WNV in individuals living in Ontario.

This study involved the secondary use of existing human health data, and was approved by the Children's Hospital of Eastern Ontario Research Ethics Board, the ICES Privacy Office, and the University of Ottawa Health Sciences and Science Research Ethics Board. Data analysis was performed using SAS 9.3 (SAS Institute, Cary, NC).

Data sources

A cohort of Ontario residents with laboratory confirmed or probable incident WNV infection was previously established for a WNV costing study [8]. In this cohort, incident WNV cases occurring between 1 January 2002 and 31 December 2012 were identified in Public Health Ontario Laboratory (PHOL) data by applying laboratory case definitions developed by Ontario's Ministry of Health [21]. Individual records in the cohort were then deterministically-linked to ICES-held (see below) health administrative databases (Discharge Abstract Database [DAD] for hospitalisations, National Ambulatory Care Reporting System [NACRS] for emergency department visits, Ontario Health Insurance Programme [OHIP] for ambulatory physician visits, Ontario Drug Benefits Programme [ODB] which provides information on drug claims history, ICES cohorts and registries and demographic datasets [Registered Persons Database (RPDB)]. ICES is an independent, non-profit, research organisation that is a repository for many population-based health databases in Ontario (www.ices.on.ca). As a prescribed entity under Ontario's privacy legislation, ICES is authorised to collect and use health care data for the purposes of health system analysis, evaluation and decision support. Secure access to these data is governed by policies and procedures that are approved by the Information and Privacy Commissioner of Ontario.

These datasets were linked using unique encoded identifiers and analysed at ICES. Additional details for these datasets can be found in Supplementary Table S1.

Outcome ascertainment

ICES-held health administrative data were used to ascertain outcomes (i.e. development of WNND) and chronic disease prevalence in the WNV cohort, in addition to information on age and sex. WNND outcomes were identified by searching for any records with at least one physician billing code (modified ICD-9 code in OHIP) or International Classification of Diseases, 10th Revision, with Canadian Enhancements (ICD-10-CA) diagnostic code (in NACRS and/or DAD) indicating encephalitis, meningitis, acute flaccid paralysis, or a combination of these conditions within ±30 days of the WNV infection index date (previously estimated in the costing study as 14 days prior to the earliest recorded laboratory date – see [8]). All codes can be found in Supplementary Table S2.

Risk factor definition

Thirteen comorbid conditions were evaluated as risk factors for the development of WNND. Ten comorbidities were selected due to their inclusion in previous similar studies (i.e. cancer [10, 14–17], congestive heart failure (CHF) [3, 10, 14, 15, 17], chronic obstructive pulmonary disease (COPD) [15, 16], chronic renal disease (CRD) [10, 14–17], diabetes [10, 14–17], human immunodeficiency virus (HIV) [10, 14–16], hypertension [10, 14–17], [recipient of] organ transplant [10, 14–16], rheumatoid arthritis [10], and stroke [10, 14–16]). Additionally, Alzheimer's disease and/or dementia and asthma were included based on their prevalence in Ontario (7.5% [ages 65 years and older] and 12.9% [ages 1 year and older], respectively [2016 prevalence] [22]) and multiple sclerosis (MS) was included due to its association with neurotropic disease [23]. Comorbid conditions in the WNV cohort were identified by: (1) extracting records of prevalent/incident conditions from pre-existing disease-specific registries or ICES-derived cohorts; or (2) applying algorithms designed to identify conditions in health administrative data through the satisfaction of multiple criteria (only used when a pre-existing registry or derived cohort was not available). Validated algorithms were available for CRD [24], MS [25], and Alzheimer's/dementia (Ontario residents aged 65 years and older) [26]; the stroke algorithm was developed for this study with input from specialists. The other nine comorbid conditions had records extracted from derived cohorts or existing registries. Charlson Comorbidity Index (CCI) scores were calculated using an established algorithm [27]. Seventeen conditions were included in the CCI calculation (i.e. myocardial infarction, CHF, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, diabetes or diabetes with chronic complication, haemiplegia or paraplegia, renal disease, any malignancy [including leukaemia and lymphoma], moderate or severe liver disease, metastatic solid tumour, AIDS/HIV). There is some overlap between CCI comorbidities and the individual comorbidities evaluated in this study, but many definitions for CCI conditions were too broad for their respective conditions to be included as independent variables.

Data analysis

We performed a descriptive analysis using counts and proportions to explore demographic and health-related baseline characteristics of the study population (overall and by specific WNND manifestation). Individuals with any WNND manifestation were classified as having WNND, while those without any WNND manifestation were classified as not having WNND. Individuals with a specific WNND manifestation (i.e. WNE, WMN, or WNP) were classified as having the relevant WNND outcome regardless of whether they also had another WNND manifestation; individuals without the specific WNND manifestation were classified as not having the specific outcome and included in the denominator for analyses. Chi-square and Fisher's exact tests were used to identify factors associated with WNND and specific WNND manifestations, and cumulative incidence rates were calculated (bivariable analysis results for WNM and WNP are not shown, but are available in Supplementary Tables S3 and S4). Only risk factors significantly associated with the outcomes were displayed in the results and used in subsequent analyses. For the risk factor analysis, we used log binomial

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regression to compute risk ratios (RR) and 95% confidence intervals (CI) comparing risk of WNND and WNE with respect to comorbidities (note – results tables for WNM and WNP are not shown, but are available as Supplementary Tables S5 and S6 because comorbid conditions [or age or sex] were not significantly associated with those outcomes during the analysis). Study variables (i.e. 13 chronic conditions and age and sex [note – HIV and recipient of organ transplant were combined into one variable, 'immunocompromised', due to small case numbers]) were first assessed in bivariable analyses with the outcome; those associated at a P-value <0.20 were entered into multivariable log binomial models. Backward selection was used to remove non-significant ($P < 0.05$) variables until a final model was achieved. Variables were removed one-by-one starting with those with the largest P-values; after the removal of each variable, the fit of the model was evaluated using likelihood ratio tests (test value <0.05 indicated a better fit). Final model comorbid variables were tested as interaction terms with age and sex. CCI scores were evaluated in separate models (due to collinearity concerns from overlap between study variables and variables included in CCI measurement) that included the variables age and sex.

Results

Between 2002 and 2012, 1884 incident, laboratory-confirmed and probable WNV-infected individuals were identified in the PHOL dataset and individually linked to health administrative databases (Table 1). Of these, 18.3% ($n = 345$) developed WNND, with most developing only one manifestation (87.8%, $n = 303$). There were no records of all three WNND manifestations (i.e.WNE, WNM, and WNP) developing in a single individual.

Of those who developed WNND, 53.9% ($n = 186$) were male and 68.7% ($n = 237$) were 45 years of age or older (median age was 56 years). More than half (55.4%, $n = 191$) of individuals who developed WNND had one or more comorbid conditions, and 40.8% had a CCI score of ≥1. The most common comorbidities among individuals with WNND were hypertension (38.3%, $n = 132$) and diabetes (18.0%, $n = 62$).

In initial bivariable analyses, WNND and WNE were significantly associated ($P < 0.05$) with a number of individual characteristics and chronic conditions (Table 2); the incidence of both were significantly increased among males, older individuals, and among those with ≥1 chronic condition. WNND was also associated with a CCI score of ≥1, CHF, diabetes, hypertension, immunocompromised, and stroke; WNE was associated with CHF, COPD, CRD, diabetes, hypertension, and stroke. WNM and WNP were not significantly associated with age, sex or any comorbid conditions (see Supplementary Tables S3 and S4). As WNE was driving WNND associations, we present only WNE multivariable results below. However, the CCI multivariable analysis includes WNM and WNP because chronic conditions included in that index but not as independent variables in this study may have associations with WNM and WNP.

Seven comorbid conditions (CHF, COPD, diabetes, hypertension, immunocompromised, CRD, stroke) and age and sex were associated with development of WNE in bivariable regression analyses (Table 3). Multivariable regression modelling identified immunocompromised, age, and sex as independent risk factors for WNE. Specifically, individuals who had had an organ

Table 1. Descriptive characteristics of WNV-infected individuals in the study population

Characteristic	Number ($n = 1884$)	Proportion (%)
Sex		
Female	988	52.4
Male	896	47.6
Age (age categories; years)		
Under 18	95	5.0
18–44	616	32.7
45–64	791	42.0
65–79	312	16.6
80 and older	70	3.7
Age (mean ± S.D.; years)	49.3 (±18.1)	–
Any chronic condition		
Yes	887	47.1
No	997	52.9
Charlson Comorbidity Index score		
0: no comorbidities	1459	77.4
1–3: low	320	17.0
4–6: medium	73	3.9
7+: high	32	1.7
Alzheimer's disease and/or dementia	11	0.6
Asthma	261	13.9
Cancer (within two years prior to WNND diagnosis)	36	1.9
CHF	53	2.8
COPD	134	7.1
CRD	39	2.1
Diabetes	221	11.7
HIV[a]	–	–
Hypertension	576	30.6
MS[a]	–	–
Recipient of organ transplant[a]	–	–
Rheumatoid arthritis	36	1.9
Stroke (within six months prior to WNND diagnosis)	26	1.4
Any WNND[b]	345	18.3
West Nile encephalitis	176	9.3
West Nile meningitis	145	7.7
West Nile acute flaccid paralysis	66	3.5

Abbreviations: CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CRD, chronic renal disease; HIV, human immunodeficiency virus; MS, multiple sclerosis; S.D., standard deviation; WNND, West Nile neuroinvasive disease; WNV, West Nile virus.

[a]HIV, multiple sclerosis, and recipient of organ transplant counts not shown due to small cell counts (<6).

[b]Number of individuals with WNND, any manifestation/s. For example, a patient with WNE and WNM would be counted here only once. The rows (manifestations) below are not mutually exclusive, as individuals could have had more than one manifestation.

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Table 2. Bivariable analyses for overall WNND and for WNE, with other characteristics[a]

Characteristic[b]	WNND			WNE		
	Yes (%)[c,d] *n* = 345	No (%)[c,d] *n* = 1539	Cumulative incidence per 100 (95% CI)[e]	Yes (%)[c,d] *n* = 176	No (%)[c,d] *n* = 1708	Cumulative incidence per 100 (95% CI)[e]
Sex						
Female	159 (46.1)	829 (53.5)	16.1 (13.9–18.5)	75 (42.6)	913 (53.5)	7.6 (6.0–9.4)
Male	186 (53.9)	710 (45.8)	20.8 (18.2–23.6)	101 (57.4)	795 (46.5)	11.3 (9.3–13.5)
Age (age categories; years)						
Under 18	27 (7.8)	68 (4.4)	28.4 (19.6–38.6)	13 (7.4)	82 (4.8)	13.9 (7.5–22.3)
18–44	81 (23.5)	535 (34.8)	13.1 (10.6–16.1)	32 (18.2)	584 (34.2)	5.2 (3.4–7.3)
45–64	120 (34.8)	671 (43.6)	15.2 (12.7–17.9)	48 (27.3)	743 (43.5)	6.1 (4.5–8.0)
65–79	91 (26.4)	221 (14.4)	29.2 (24.2–34.6)	62 (35.2)	250 (14.6)	19.9 (15.6–24.7)
80 and older	26 (7.5)	44 (2.9)	37.1 (25.9–49.5)	21 (11.9)	49 (2.9)	30.0 (19.6–42.1)
Age (mean, S.D.; years)	53.2 (21.3)	48.4 (17.2)	–	57.4 (22.1)	48.4 (17.5)	–
Charlson Comorbidity Index Score						
0: none	204 (59.1)	1255 (81.6)	14.0 (12.2–15.9)			
1–3: low	95 (27.5)	225 (14.6)	29.7 (24.7–35.0)			
4–6: medium	29 (8.4)	44 (2.9)	39.7 (28.5–51.9)	–	–	–
7+: high	17 (4.9)	15 (1.0)	53.1 (34.7–70.9)			
Any chronic condition						
Yes	191 (55.4)	696 (45.2)	21.5 (18.9–24.4)	106 (60.2)	781 (45.7)	12.0 (9.9–14.3)
No	154 (44.6)	843 (57.8)	15.4 (13.3–17.8)	70 (39.8)	927 (54.3)	7.0 (5.5–8.8)
Asthma	45 (13.0)	216 (14.0)	17.2 (12.9–22.4)	24 (13.6)	237 (13.9)	9.2 (6.0–13.4)
Cancer[e]	9 (2.6)	27 (1.8)	25.0 (12.1–42.2)	–	–	–
CHF	21 (6.1)	32 (2.1)	39.6 (26.5–54.0)	15 (8.5)	38 (2.2)	28.3 (16.8–42.4)
COPD	33 (9.6)	101 (6.6)	24.6 (17.6–32.8)	19 (10.8)	115 (6.7)	14.2 (8.8–21.3)
CRD	11 (3.2)	28 (1.8)	28.2 (15.0–44.9)	10 (5.7)	29 (1.7)	25.6 (13.0–42.1)
Diabetes	62 (18.0)	159 (10.3)	28.1 (22.2–34.5)	39 (22.2)	182 (10.7)	17.6 (12.9–23.3)
Hypertension	132 (38.3)	444 (28.8)	22.9 (19.5–26.6)	77 (43.2)	499 (29.2)	13.4 (10.7–16.4)
Immunocompromised[f]	–	–	–	–	–	–
Rheumatoid arthritis[f]	7 (2.0)	29 (1.9)	19.4 (8.2–36.0)	–	–	–
Stroke	9 (2.6)	17 (1.1)	34.6 (17.2–55.7)	6 (3.4)	20 (1.2)	23.1 (9.0–43.7)

Abbreviations: CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CRD, chronic renal disease; MS, multiple sclerosis; S.D., standard deviation; WNE, West Nile encephalitis; WNND, West Nile neuroinvasive disease.
[a]WNM and WNP tables are shown in Additional File 3 and Additional File 4 because there were no significant associations ($P < 0.05$) with age, sex, or comorbid conditions.
[b]Alzheimer's disease/dementia and MS not shown because cell counts were <6 for WNND and WNE.
[c]Column percentages.
[d]Row percentages.
[e]Immunocompromised not shown to preclude calculation of small cell counts.
[f]Immunocompromised, rheumatoid arthritis, and cancer not shown for WNE because cell counts were <6.

transplant or who were living with HIV (i.e. immunocompromised) had a 161% (aRR 2.61 [95% CI 1.23–4.53]) relative increase in risk for WNE; and each 1-year increase in age was associated with a 2% (aRR 1.02 [95% CI 1.02–1.03]) relative increase in risk, while males had a 32% (aRR 1.32 [95% CI 1.00–1.76]) relative increase in risk compared to females.

Multivariable regression analysis that included the CCI also included the variables age and sex (Table 4). There was a significant increase in risk for developing WNND for individuals with any CCI score not equal to zero. For those with a CCI score between 1 and 3, there was a 98% (aRR 1.98; 95% CI 1.57–2.48) relative increase in risk of WNND compared to those with a CCI score of 0, while those with scores between 4 and 6 or 7 or more had a 163% (aRR 2.63; 95% CI 1.86–3.56) and a 245% (aRR 3.45; 95% CI 2.25–4.83) relative increase in risk of WNND, respectively, compared to those with a CCI score of 0. Age remained associated with WNND, with an adjusted RR of 1.01 (95% CI 1.00–1.01).

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Table 3. Unadjusted and adjusted risk ratios for WNE

Characteristic	Unadjusted RR, 95% CI	Adjusted RR, 95% CI
Sex		
Female	Ref.	Ref.
Male	1.48 (1.12–1.98)	1.32 (1.00–1.76)
Age at time of WNE development (continuous variable, years)	1.03 (1.02–1.04)	1.02 (1.02–1.03)
Alzheimer's Disease/ Dementia	0.97 (0.06–3.71)	–
Asthma	0.98 (0.63–1.45)	–
Cancer	1.50 (0.56–3.03)	–
CHF	3.22 (1.94–4.84)	1.47 (0.85–2.39)
COPD	1.58 (0.98–2.39)	–
CRD	2.85 (1.51–4.63)	–
Diabetes	2.14 (1.52–2.93)	1.33 (0.91–1.88)
Immunocompromised	3.88 (1.72–6.64)	2.61 (1.23–4.53)
Hypertension	1.77 (1.33–2.34)	–
MS[a]	–	–
Rheumatoid Arthritis	1.19 (0.38–2.62)	–
Stroke	2.52 (1.01–4.61)	–

Abbreviations: CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CRD, chronic renal disease; MS, multiple sclerosis.
[a]Model failed to converge.
–Not included in final model.

Table 4. Unadjusted and adjusted risk ratios for WNND with CCI score as the variable of interest

Characteristic	Unadjusted RR, 95% CI	Adjusted RR, 95% CI
Sex		
Female	Ref.	Ref.
Male	1.29 (1.07–1.56)	1.18 (0.98–1.43)
Age at time of WNND development (continuous variable, years)	1.01 (1.01–1.02)	1.00 (1.00–1.01)
CCI score		
Null (0)	Ref.	Ref.
Low (1–3)	1.86 (1.51–2.27)	1.98 (1.57–2.48)
Medium (4–6)	2.28 (1.64–3.00)	2.63 (1.86–3.56)
High (7+)	3.0 (2.02–4.02)	3.45 (2.26–4.83)

Discussion

The aim of this study was to identify comorbid risk factors for WNND in the Ontario population between 2002 and 2012. We found that WNE was driving associations with comorbid risk factors, and increased risk of WNE was associated with immunocompromised, male sex, and increasing age. CCI scores above zero increased risk of WNND, with risk increasing with CCI score severity. This is the first study to identify comorbid risk factors of WNND, specifically WNE, in a Canadian population; and our findings corroborate those of similar studies conducted on American and Greek populations within the last two decades. Immunocompromising conditions were found to increase the odds (aOR 5.6, 95% CI 2.1–14.9) of WNE in a Texas matched case-control study [14]. Age was identified as a risk factor for WNND development in a multi-state (American) study on the 2002 WNV epidemic: with individuals below the age of 40 as the reference category, relative risks increased in each 10-year age group up to the age of 89, ranging from 2.8 (95% CI 2.5–3.2) to 12.0 (95% CI 10.5–13.6) [12]. In WNND patients in the 2002 Illinois epidemic, slightly higher relative risks were reported for 10-year age groups, with ages 0–19 years as a reference; relative risks ranged from 2.4 (95% CI 1.5–3.8) in individuals aged 20–29 years to 27.5 (95% CI 18.6–40.8) in those aged 80 years and older [9]. Additionally, studies on Greek, Californian, and Coloradan populations have also suggested age as a risk factor for WNND [10, 11, 13]. Lastly, male sex was associated with a 10–80% relative increase in risk (age-dependent) of WNND in the 2002 multi-state study, while odds ratios of 1.57 (95% CI 1.18–2.09) and 3.1 (95% CI 1.5–6.4) were reported for males in the California and Greek cohorts [11, 13].

In our study, WNE was driving the relationship between WNND and comorbid conditions. Clinically, this is significant because individuals who develop WNE generally suffer more severe health outcomes than those with WNF or WNM (WNP, although rare, is regarded as the most severe manifestation). While mortality is generally <2% for WNF or WNM [9, 28–30], rates as high as ~20% have been reported for WNE [10, 17, 31] (46% in individuals ≥65 years [32]). Hospital stays are also longer, with a mean length of stay for WNE of 8–25 days [9, 28, 33], while mean length of stay for WNM and WNF is generally ≤10 days [9, 14, 17, 28, 34]. A number of studies suggest that only 20–33% of WNE patients return home without additional care or rehabilitation [10, 28, 29, 35] – the corresponding proportion for WNM and WNF is >65% [10, 28, 29, 35]. Additionally, while many individuals with WNE experience long-term neurological abnormalities (e.g. abnormal tandem gait, abnormal reflexes) that can persist for years after infection [7, 28], those with WNF or WNM have sequelae that resolve more quickly [28, 36–38].

Statistical factors related to WNE were at least partly driving the relationship between WNND and chronic comorbidities. WNE was the most common manifestation of WNND in the cohort, and therefore its analysis had greater statistical power. WNP is the rarest manifestation of WNND, and small cell sizes in our study most likely precluded meaningful analysis. Additionally, the relationship between WNE, WNND, and comorbidities may also have been affected by biological factors. The individuals who developed WNE had a mean age of nearly 60 years, while patients with WNM had a mean age almost a decade younger. This time differential may have allowed older patients to develop chronic conditions from existing health factors that were not measured in this study. For example, a number of comorbidities that develop in individuals with cardiometabolic risk factors showed some relationship with neuroinvasive disease in unadjusted analysis (e.g. CHF) (see Supplementary Table S7). Some of these risk factors (e.g. obesity) cause systemic inflammation that can impair immune system function potentially facilitating virus entry into the CNS through a weakened blood-brain barrier [39].

Although not previously reported on specifically pertaining to WNND, in individuals with influenza, higher CCI scores have been associated with more severe outcomes including intensive

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care unit admission and death [40, 41]. Interestingly, several comorbid conditions in this study that were significant in bivariable or multivariable modelling are included in the CCI (i.e. CHF, diabetes, HIV, and CRD). However, mechanisms of WNV progression to WNND are not well-studied in the context of contributing comorbid conditions. Many of the comorbidities in this study are related (e.g. hypertension and CHF) so without a better understanding of how WNV enters the central nervous system and how this is facilitated by existing conditions, identifying specific comorbid risk factors is difficult. Next steps for WNND risk factor studies should include mediation analyses, particularly on large cohorts, and inclusion of cardiometabolic risk factors as independent variables.

There were 345 cases of WNND identified in health administrative data in individuals with incident laboratory-confirmed WNV in Ontario between 2002 and 2012, with an 11-year cumulative incidence of 18.3%. It is estimated that less than 1% of WNV infections result in neurological involvement [1] – our results suggested a cumulative incidence of 18.3% for WNND. This discrepancy may reflect misdiagnosis, at least in part, of neurological illness resulting from WNV infection, and underdiagnosis of mild WNV cases, i.e. patients with West Nile fever (WNF), a more common illness resulting from WNV infection that presents with non-specific signs and symptoms and has no neurological involvement. Encephalitis, meningitis, and acute flaccid paralysis have multiple aetiologies (both viral and non-viral), so their diagnosis alone does not establish WNV as the causative agent. The non-specific nature of WNV pathogenicity makes diagnosis of WNND with a WNV aetiology difficult. A 2013 study on rates of encephalitis in Canada between 1994 and 2008 found that nearly 50% of encephalitis hospitalisations had unknown aetiologies; additionally, it [the study] identified spatio-temporal clusters of undiagnosed encephalitis hospitalisations in warmer months that could have been caused by arboviral infections [42]. A lack of physician awareness and underutilisation of serologic testing most likely contribute to underdiagnosis of both WNF and WNND in Ontario (see [43]). Pertaining to this study's results, had more WNF cases been identified and diagnosed, this would result in both more WNV cases being diagnosed and more WNND cases being correctly identified – this would better reflect epidemiological characteristics of WNV in terms of the estimated proportion of infections that progress to WNND, and may increase statistical power to detect associations between neuroinvasive disease and comorbid conditions.

A related limitation encountered during this study was the lack of an established diagnostic definition of WNND in Canada; we used an existing algorithm to identify individuals in health administrative data who were only considered a WNND case if they had a laboratory-confirmed WNV infection within ±30 days of the infection index date. Individuals who had not received a laboratory test for WNV infection but who developed encephalitis, meningitis, and/or acute flaccid paralysis were not included in the cohort. An established definition for WNND would likely aid in increasing physician awareness and utilisation of testing for WNV antigens or antibodies.

In Ontario, the consequences of WNV infections progressing to neuroinvasive disease could become more severe in the coming years due to demographic and environmental changes. As a result of population ageing [18], more people will be living with multimorbidity and chronic disease. The results of this study, and others from the United States and Greece, suggest that individuals living with comorbidities are at greater risk of developing neuroinvasive disease after infection with WNV. In addition, Ontario's climate is warming, with projections suggesting an average increase in temperature of 2.3 °C in the next 10 years under a high emissions scenario [19]. WNV vector ranges are projected to expand through southern Canada, exposing more Ontarians to WNV vectors during the warmer months [20]. The severity of WNND, the lack of a cure, costly health care expenses, Ontario's changing climate and demographics, and the current gap in understanding of how the virus progresses to neurological disease, necessitate prevention strategies that target the first step in the disease chain: infection with WNV. Public health strategies that focus on preventing infection with WNV are currently best practise for preventing WNND and can be tailored to target vulnerable groups with identified risk factors, such as those living with comorbidities and the elderly.

Individuals living with chronic disease are at higher risk for developing neurological complications following infection with WNV. Future research is needed to identify underlying biological mechanisms of the relationship between comorbid conditions and WNND risk.

Individuals with comorbid conditions are at higher risk for WNND following WNV infection.

Conclusion

We found that WNE was driving the relationship between WNND and comorbid conditions. Immunocompromised (i.e. HIV or recipient of organ transplant) is an important risk factor for developing WNE after infection with WNV. Additionally, male sex, increasing age, and increasing CCI scores also increase the risk of WNE/WNND. Our findings support evidence from previous studies on WNND risk factors, and highlight the importance in understanding the role of comorbidities in severe health outcomes of WNV infection.

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Conflict of interest. The authors declare that they have no competing interests.

Ethical standards and consent to participate. This study was approved by the Children's Hospital of Eastern Ontario Research Ethics Board and the University of Ottawa Health Sciences and Science Research Ethics Board.

Data availability statement. The dataset from this study is held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers (e.g. healthcare organisations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca). The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

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