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**Original Article**



# Original Article

# Frequency and impact of paediatric acute-onset neuropsychiatric syndrome/paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections diagnosis in Canada

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## ABSTRACT

**Objectives:** This study aims to estimate the prevalence of the PANS/PANDAS diagnostic label in Canada and describe its impact on families, patients, and health care.

**Methods:** Through the Canadian Paediatric Surveillance Program (CPSP), a monthly form was distributed to paediatricians from December 2019 to November 2021, requesting reports of children who received the diagnostic label of PANS/PANDAS between the ages of 3 and 18 years seen in the previous month. Descriptive and association statistical analyses were performed.

**Results:** Eighty-four cases (57% female, median age of symptom onset 7.8 years interquartile range [IQR] = 5) who received the diagnostic label of PANS/PANDAS were included. Prevalence was found to be 1 in 60,155 (0.0017%). Core diagnostic criteria for PANS/PANDAS (obsessive-compulsive disorder or tics or acute food refusal) were not present in 12% of cases (10/84). Only 22% reported sudden symptom onset. Infection was associated with symptom onset or exacerbation in less than one-third of cases. The majority exhibited two or more neuropsychiatric symptoms (95%). There was significant health care utilization and symptom burden amongst cases. There was a significant difference in the certainty of diagnosis between physicians and families ($P < 0.05$).

**Conclusions:** PANS/PANDAS diagnoses, while rare, significantly impact children, families, and the health care system. Diagnostic uncertainty underscores the challenges professionals and families face in accessing effective care, emphasizing the need for education and evidence-based clinical practice guidelines.

**Keywords:** *Pediatric acute-onset neuropsychiatric syndrome*; *Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections*; *Population surveillance*; *Prevalence*.

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Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) is a syndromal diagnosis characterized by abrupt onset and episodic course of neuropsychiatric symptoms associated with infection. The original publication describes five criteria required for the diagnosis of PANDAS: the presence of a tic disorder and/or obsessive-compulsive disorder (OCD), onset between 3 years of age and peri-puberty, abrupt onset with episodic course, temporal association with group A Streptococcus (GAS) infection, and association with neurologic abnormalities (1). A more recent publication defines a broader diagnostic entity, pediatric acute-onset neuropsychiatric syndrome (PANS). Criteria include abrupt nature of the onset of OCD and/or avoidant/restrictive food intake disorder (ARFID) with concurrent presence of at least two neuropsychiatric symptoms, such as anxiety, depression, irritability, behavioural regression, sudden deterioration in school performance, motor or sensory abnormalities, and somatic signs and symptoms. Additionally, it is specified that symptoms are not better explained by a known neurologic or medical disorder such as Sydenham Chorea, Systemic Lupus Erythematosus, Tourette disorder, or others (2). The umbrella term PANS/PANDAS is often used in current literature, as well as in this article.

Considerable debate has surrounded these diagnostic entities (3–7). Only one recently published study from the USA has attempted to elucidate the frequency of these conditions (8). At the heart of the definition is the concept that the symptoms are driven by an inflammatory process, and therefore may respond to therapies directed at the immune system (9–13). However, there is no widely accepted diagnostic test or biomarker for these conditions, and there are challenges in the application of published clinical diagnostic criteria (3). For example, the significant symptom overlap with other psychiatric and neurological disorders makes differential diagnosis particularly difficult. Establishing a clear temporal relationship between infection and symptom onset can be challenging, especially in cases with a more gradual onset, which complicates the diagnostic process (6,8). In addition, clear evidence of effectiveness for treatments is lacking (3–7). This uncertainty regarding frequency, diagnosis, and treatment leaves health care providers with limited evidence to guide practice, and sometimes reluctance to assess and treat patients who may have these conditions (14). In fact, there are limited published data on clinical practice patterns in diagnosis, assessment, and treatment (3,7).

The aims of this study were 1) to estimate the prevalence of PANS/PANDAS diagnosis in children in Canada, 2) to describe clinical characteristics of patients who received PANS/PANDAS diagnosis, 3) to determine practice patterns for patients receiving these diagnoses, and 4) to understand the family, patient and health care burden associated with these diagnoses.

## METHODS

The Canadian Paediatric Surveillance Program (CPSP) is a partnership between the Canadian Pediatric Society (CPS) and the Public Health Agency of Canada (PHAC) whose mandate is to provide surveillance of rare ("low frequency") and high-impact conditions of childhood. Through the established methodology of the CPSP, over 2700 paediatricians and pediatric subspecialists practicing across Canada were actively surveyed on a monthly basis between December 1, 2019, and November 30, 2021, to report patients meeting the following case definition: "any child between the ages of 3 years and 18 years (up to the 18th birthday), seen in the previous month who has received the diagnostic label of PANDAS or PANS." Study cases were inclusive of all children who had received a PANS/PANDAS diagnosis at any time, by any health care provider or a family member, regardless of the diagnosis made by the physician reporting the case. Cases were not included or excluded based on whether they did or did not meet published clinical criteria for diagnosis.

Respondents who identified cases were sent a detailed questionnaire, which included questions about demographics (age, gender, location), clinical presentation, laboratory tests completed, treatments received by the patient, health care burden (number and type of providers involved, hospitalizations), and patient and family impacts (school absences, missed work, expenses). Questionnaires were returned to the CPSP, were de-identified, and uploaded to a secure PHAC portal. The study team was provided access to the data for analysis.

The full case report form and study protocol are accessible at https://www.cpsp.cps.ca/surveillance/concluded-studies. The study was approved by The Hospital for Sick Children and the PHAC Research Ethics Boards. Of note, Quebec privacy legislation prohibits the sharing of information, and detailed information for cases reported by physicians working in Quebec was therefore unavailable.

### Statistical analysis

The minimum prevalence of children receiving a PANS/PANDAS diagnosis was calculated using the total Canadian population (excluding Quebec) of children aged 3 to 18 years in the calendar year 2021 as the denominator. Demographic and clinical data were analyzed using RStudio v1.2.1 (15). The median and interquartile range (IQR) were used for continuous variables. Frequencies and percentages were reported for categorical variables. Chi-square and Fisher's exact tests were used to assess discordance between physician and family diagnostic certainty as well as the involvement of complementary health care providers ($P < 0.05$). Cells with counts between one and four were represented as <5 or omitted in order to preserve privacy. All survey data were included in analyses, regardless of survey completeness.

## RESULTS

### Prevalence

Ninety-nine children who had received the diagnostic label of PANS/PANDAS were identified between December 1, 2019, and November 30, 2021. One was determined to be a duplicate and 14 were excluded (from a physician practicing in Quebec, or because a case report form/questionnaire was not submitted), resulting in a study group of 84 cases. Extrapolating the total population of children ages 3 to 18 years old in Canada, minus the province of Quebec (2021, 5,050,850), the minimum prevalence of the diagnosis of PANS/PANDAS in Canada in children aged 3 to 18 years was 1 in 60,155 (0.0017%) (16).

### Demographics

Cases were most frequently identified by psychiatrists (26/84, 31%), general paediatricians providing consultative care (23/84, 27%), general paediatricians providing primary care (20/84, 24%), and pediatric neurologists (11/84, 13%; Table 1). Providers identifying cases practiced in a variety of practice settings, including outpatient clinics (65/84, 79%), private offices (10/84, 12%), and inpatient hospital units (7/84, 8.5%). Cases were identified predominantly in Alberta (45/84, 54%), Ontario (31/84, 37%), and British Columbia (5/84, 6%).

The median age of symptom onset was 7.8 years (IQR = 5; range 2 to 16 years). PANS/PANDAS was more often diagnosed in females (48/84, 58%). Seventy percent of cases had one or more pre-existing conditions (prior to the onset of PANS/PANDAS symptoms), including anxiety and/or depression (26/84, 31%), OCD (25/84, 30%), attention deficit hyperactivity disorder (24/84, 30%), and autism spectrum disorder (13/84, 15.5%; Table 2).

### Clinical presentation

Table 2 illustrates the clinical characteristics of the study group. Core diagnostic criteria for PANS/PANDAS (OCD or tics or acute food refusal) were not present in 12% of cases (10/84). At initial presentation, 74% had one or more OCD symptoms (62/84), 39% had tics (33/84), and 36% (30/84) had acute food refusal. Symptom onset was described as abrupt (<24 hours) in 23% (19/84) and gradual in 77% (65/84). A microbiologically confirmed GAS infection was associated with symptom onset in 22/84 (26%) cases and with symptom exacerbation in 25/84 (30%) cases. A documented infection other than GAS was associated with symptom onset in 10/84 (12%) and with symptom exacerbation in 14/84 (17%) cases. In 64% (54/84) and 56% (47/84) of cases, respectively, symptom onset or exacerbation was not associated with infection. Over 95% (80/84, 95%) of cases presented with 2 or more neuropsychiatric symptoms, with the average case exhibiting more than 6 neuropsychiatric symptoms (median = 6.5, IQR = 4) (Table 2).

**Table 1.** Demographics of physicians who identified PANS/PANDAS cases (n = 84)*

| | n | % |
|---|---|---|
| Province of submitting provider* | | |
| Alberta | 45 | 53.6 |
| Ontario | 31 | 36.9 |
| British Columbia | 5 | 6.0 |
| Discipline of submitting provider | | |
| Psychiatrist | 26 | 30.9 |
| General Paediatrician (consultative care) | 23 | 27.4 |
| General Paediatrician (primary care) | 20 | 23.8 |
| Pediatric Neurologist | 11 | 13.1 |
| Other† | 8 | 9.5 |
| Practice setting of submitting provider | | |
| Outpatient clinic | 65 | 79.3 |
| Private office | 10 | 12.2 |
| Inpatient hospital | 7 | 8.5 |

Partially completed surveys were included in the analysis, so the number of respondents varied between questions.
*Due to CPSP privacy regulations, variables less than 5 are not reported;
†Other included (in descending order): developmental pediatrics, adolescent medicine, pediatric emergency medicine, and pediatric nephrology

### Clinical evaluation, treatment, and burden

Details of the clinical evaluation, treatments, and burden can be found in Tables 3 and 4. Diagnostic investigations were completed in 80% of cases, including antistreptolysin O titre (ASOT) (53/84, 63%), throat culture for GAS (35/84, 42%), and bloodwork (any of Complete Blood Count, Erythrocyte Sedimentation Rate, C-Reactive Protein, Antinuclear Antibody, 56/84, 67%). A diagnosis of PANS/PANDAS was made by physicians in 64% of cases, most commonly by a psychiatrist (39/84, 46%), general paediatrician (25/84, 30%), or subspecialty paediatrician (19/84, 23%). Subspecialists represented a broad range of disciplines, including adolescent medicine, emergency medicine, nephrology, neurology, and rheumatology. The remainder of the diagnoses (36%) were made by a complementary health care provider or lay person (parent, teacher). Approximately 76% (52/68) of cases had five or more

**Table 2.** Demographic and clinical characteristics of PANS/PANDAS cases (n = 84)*

| | n | % |
|---|---|---|
| Female | 48 | 58% |
| Age of onset | 7.8 years, IQR = 5 | NA |
| Pre-existing diagnosis | | |
| Anxiety/depression | 26 | 31.0 |
| Obsessive-compulsive disorder | 25 | 29.8 |
| Attention deficit/hyperactivity disorder | 24 | 28.6 |
| Autism Spectrum Disorder | 13 | 15.5 |
| Developmental disorder | 5 | 6.0 |
| Neuropsychiatric symptoms | | |
| Emotional lability | 67 | 79.8 |
| Irritability/agitation | 63 | 75.0 |
| Anxiety | 60 | 71.4 |
| Aggression | 45 | 53.6 |
| Sleep disturbance | 41 | 48.8 |
| Sensory hyperactivity | 35 | 41.7 |
| Deterioration in school performance | 34 | 40.5 |
| Behavioural regression | 33 | 39.3 |
| Depression/low mood | 30 | 35.7 |
| Food refusal | 30 | 35.7 |
| Hyperactivity | 25 | 29.8 |
| Severely oppositional behaviours | 23 | 27.4 |
| Urinary frequency | 18 | 21.4 |
| New onset enuresis | 16 | 19.0 |
| Fine motor/handwriting deterioration | 13 | 15.5 |
| Hallucinations | 7 | 8.3 |
| Clumsiness | 7 | 8.3 |

IQR, interquartile range; NA, not applicable
*Due to CPSP privacy regulations, variables less than 5 are not reported.

**Table 3.** Diagnostic investigations and treatments in PANS/PANDAS cases (n = 84)*

| | n | % |
|---|---|---|
| Tests for group A streptococcal infection | | |
| ASOT | 53 | 63.1 |
| Throat culture for group A strep | 35 | 41.7 |
| Anti-DNase | 11 | 13.1 |
| Rapid strep test | 5 | 6 |
| None | 19 | 22.6 |
| Other medical tests | | |
| Bloodwork | 56 | 67 |
| Neuroimaging (CT or MRI) | 20 | 23.8 |
| EEG | 17 | 20.2 |
| Other** | 10 | 11.9 |
| None | 19 | 22.6 |
| Mental health treatment | | |
| Psychotropic medication | 45 | 53.6 |
| Psychological treatment | 32 | 38.1 |
| Both therapy and medication | 22 | 26.0 |
| Treatment for infection | | |
| Antibiotic treatment for GAS | 41 | 48.8 |
| Antibiotic prophylaxis for GAS | 20 | 23.8 |
| Antibiotic eradication of GAS carriage | 13 | 15.5 |
| Tonsillectomy | 3 | 3.6 |
| Other† | 18 | 21.4 |
| None | 12 | 14.3 |
| Anti-inflammatory/immune-modulating treatment* | | |
| NSAIDs | 40 | 47.6 |
| IVIG | 6 | 7.1 |
| Other‡ | 7 | 9.5 |
| None | 29 | 34.5 |

Partially completed surveys were included in the analysis, so the number of respondents varied between questions. ASOT, antistreptolysin O Titre;
*Due to CPSP privacy regulations, variables less than 5 are not reported;
**Other included (in descending order): ECG, PET scan, folate receptor antibodies, and spine X-ray;
†Other included (in descending order): Other antibiotics for unreported reasons;
‡Other included (in descending order): diets, supplements and rituximab

health care visits since symptom onset, with 31% (24/78) involved with more than five different health care providers.

Regarding treatment, 75% of reported cases received interventions for mental health symptoms, including psychological treatment (32/84, 38%), psychotropic medication (45/84, 54%), or a combination of both (22/84, 26%). Approximately 60% (50/84) saw or were referred to at least one mental health professional; psychiatrist (56/84, 67%); or psychologist (29/84, 35%). Eighty-one percent received treatments for PANS/PANDAS which targeted infection (antibiotics, tonsillectomy). Treatments targeting inflammation (non-steroidal anti-inflammatory drugs, corticosteroids, intravenous immunoglobulin, and others) were received in 57% (48/84) of cases (see Table 3 for details).

Respondents to the survey identified adverse consequences in 82 of 84 cases, including adverse personal and family impacts, with 66% reporting new family stress, mental health concerns, or conflict (54/82) and 52% reporting significant school absences (43/82).

**Table 4.** Health burden in PANS/PANDAS cases since symptom onset (n = 84)*

| | n | % |
|---|---|---|
| Individual who determined the diagnosis | | |
| Psychiatrist | 39 | 46.4 |
| General Paediatrician | 25 | 29.8 |
| Subspecialty Paediatrician | 19 | 22.6 |
| Family member | 14 | 16.7 |
| Primary care practitioner | 13 | 15.5 |
| Complementary/alternative health care provider | 12 | 14.3 |
| Other† | 5 | 6.0 |
| Other health care providers involved | | |
| General Paediatrician | 60 | 71.4 |
| Psychiatrist | 56 | 66.7 |
| Complementary/Alternative Health Provider | 45 | 53.6 |
| Psychologist | 29 | 34.5 |
| Neurologist | 22 | 26.2 |
| Rheumatologist | 7 | 8.3 |
| Other‡ | 18 | 21.4 |
| Number of health care visits | | |
| <5 | 16 | 19.0 |
| 5–10 | 12 | 14.3 |
| 11–20 | 7 | 8.3 |
| >20 | 33 | 39.3 |
| Number of health care providers | | |
| <5 | 54 | 64.3 |
| 5–10 | 19 | 22.6 |
| 11–20 | 3 | 3.6 |
| Services accessed | | |
| Emergency department | 29 | 34.5 |
| Hospital inpatient medical admission | 8 | 9.5 |
| Psychiatric admission | 8 | 9.5 |
| Travel out of province for management | 5 | 6.0 |
| Travel out of the country for management | 3 | 3.6 |
| Impact of symptoms | | |
| Family stress | 54 | 64.2 |
| School absences | 43 | 51.1 |
| Withdrawal from activities/friends | 33 | 39.2 |
| Decline in school achievement | 28 | 33.3 |
| Withdrawal from sports/physical activity | 11 | 13.0 |
| Financial burden | 8 | 9.5 |
| Other§ | 6 | 7.1 |
| None | 5 | 6.0 |

Partially completed surveys were included in the analysis, so the number of respondents varied between questions.
*Due to CPSP privacy regulations, variables less than 5 are not reported;
†Other included (in descending order): Emergency medicine, family physician, and teacher;
‡Other included (in descending order): Developmental paediatrician, geneticist, allergist, urologist, social worker, functional medicine doctor, functional neurologist, and sotolaryngologist;
§Other included (in descending order): Fatigue, regression in development, and avoidant/restrictive food intake disorder (ARFID)

### Physician-family diagnostic concordance

There was a significant difference between the physician's perception and the physician's impression of family perception

**Table 5.** Distribution of physician and family diagnostic certainty in PANS/PANDAS cases (n = 84)

| | Physician | | Family | | Difference between physician and family certainty |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Ruled out/do not believe | 12 | 14.2 | 4 | 4.7 | P < 0.05 |
| Unlikely | 20 | 23.8 | | | |
| Uncertain | 14 | 16.6 | 15 | 18.5 | |
| Somewhat believe/likely | 36 | 42.8 | 16 | 19.8 | |
| Strongly believe | | | 34 | 41.9 | |
| Certain | 2 | 2.4 | 12 | 14.8 | P < 0.05 |

**Table 6.** Concordance and discordance in diagnostic certainty between physicians and families in PANS/PANDAS cases (n = 84)

| Family | Physician | n = 84 | % |
|---|---|---|---|
| Concordance | | 38 | 45.2* |
| Diagnosis of PANS/PANDAS likely | | 35 | 92.1** |
| Diagnosis of PANS/PANDAS unlikely | | 3 | 7.9** |
| Discordance | | 29 | 34.5* |
| Diagnosis of PANS/PANDAS likely | Diagnosis of PANS/PANDAS unlikely/uncertain | 27 | 93.1*** |
| Diagnosis of PANS/PANDAS unlikely/uncertain | Diagnosis of PANS/PANDAS likely | 2 | 7.4*** |

*Percent of total;
**percent of concordance;
***percent of discordance

with respect to certainty of diagnosis (Table 5). In 42% of the cases, there was concordance, with physicians perceiving agreement with families that a diagnosis of PANS/PANDAS was likely (35/84). Physicians reported diagnostic discordance with families in 34% of the cases, with nearly all disagreements representing situations where the physician perceived that the family believed the child had PANS/PANDAS, but the physician did not (27/29, 93%; Table 6). The involvement of complementary health care providers in the diagnostic process was significantly associated with physician reports of diagnostic discordance, where physicians identified PANS/PANDAS diagnosis as unlikely while reporting that families considered the diagnosis to be likely.

## DISCUSSION

Our study suggests a minimum prevalence of PANS/PANDAS diagnosis in Canada of approximately 1 in 60,155 (0.0017%). This surveillance study relied on physician self-reporting of cases and almost certainly represents an underestimate of prevalence. The study did not systematically survey all physicians who might encounter patients with PANS/PANDAS and cases were reported only from three provinces (Ontario, Alberta, and BC) during the study period. This may represent the regional clustering of physicians who specifically provide care for patients with PANS/PANDAS. Additionally, this lack of broader geographic case representation likely reflects incomplete reporting of cases. It is also worth noting that the coronavirus 2019 (COVID-19) pandemic and associated containment policies significantly impacted the nature of patient care, likely impeded case reporting among health care professionals during the study period, and reduced the transmission of respiratory infections, potentially contributing to an underestimation of PANS/PANDAS prevalence. In addition, the COVID-19 pandemic has been thought to impact presentations for mental health concerns. To our knowledge, the only other study to estimate the overall incidence of PANS/PANDAS in North America indicated a rate of 1 in 11,765 for children aged 3 to 12 years, with some regional variation (8). Previous studies have suggested that PANS/PANDAS is more frequent in children with certain underlying conditions: the prevalence of PANS/PANDAS was estimated to be 11% in a tic disorder cohort (n = 80, 11% abrupt symptom onset), 5% in youth attending an outpatient OCD clinic, and 1% in children followed at a movement disorders clinic (17–20).

In this study, children frequently received the label of PANS/PANDAS despite not meeting the published diagnostic criteria. For example, symptom onset was sudden (<48 hours) in only 23% of cases. Symptom onset or exacerbation was not associated with infection in more than half of cases. Importantly, the key diagnostic criteria, obsessive-compulsive symptoms, tics, or acute food refusal, were not reported in 12% of cases. These results may reflect a lack of familiarity with the diagnostic criteria on the part of both health care providers and parents or the non-specific nature of the diagnostic criteria. In addition, information in the media/online likely influences family perceptions regarding diagnosis and diagnostic criteria. Despite a significant proportion of the reported cases not meeting the diagnostic criteria for PANS/PANDAS, this is a complex population of patients, with significant and impairing neuropsychiatric symptoms, who need support and care.

We also report a significant discrepancy between health care providers and families in terms of reported confidence/certainty regarding the diagnosis of PANS/PANDAS. The discordance was almost completely accounted for by cases in which the physician reported that the family believed the diagnosis of PANS/

PANDAS to be likely, while the physician felt the diagnosis was unlikely. In fact, in our study, physicians reported being uncertain or feeling the diagnosis was unlikely in almost half of cases. More than half of the children in this cohort were seen by a complementary health care provider. The involvement of complementary health care professionals was significantly associated with diagnostic discordance. The discordance seen between families and physicians may be related to the lack of clarity regarding diagnostic criteria, challenges for families in accessing care, and conflicting information widely available to families through media and internet sources. In Canada, there are very few specialized multidisciplinary clinics available to assess patients with a concern of possible PANS/PANDAS. Physicians, particularly paediatricians and family physicians, may not have been exposed to PANS/PANDAS or even childhood OCD during their medical training or in practice and may feel unprepared to make these diagnoses and treatment recommendations. This uncertainty may be compounded by the lack of clarity regarding diagnostic criteria and limited evidence for treatments. These factors leave health care providers and families struggling to find the best path forward.

This study illustrates the emotional burden and impacts of the symptoms associated with PANS/PANDAS diagnosis on the child, family, and health care system. The majority of cases had other pre-existing diagnoses and the average case in our study population presented with more than six neuropsychiatric symptoms. This symptom profile is in line with previous samples of patients with PANS/PANDAS that describe a complex constellation of neuropsychiatric symptoms (21,22). These are clearly children, youth, and families in need of care and support. In line with previous research on children with comorbid psychiatric diagnoses, our sample demonstrated considerable utilization of health care resources (21,22). Children with mental health disorders have a significantly higher number of primary and subspecialty health care visits during the initial phases of diagnosis, followed by persistently high levels of subspecialty appointments even after the diagnosis has been made (23). It is not surprising, then, that families of patients with possible PANS/PANDAS seek multiple referrals to primary and specialty physicians, including presentations to the emergency department, admissions to the hospital, and outpatient visits. Challenges in diagnosis, lack of clarity regarding treatment pathways, and strong beliefs amongst both families and health care providers may lead families to seek multiple opinions to find relief for their child's distress and functional impairment.

Our study has several strengths, including its use of a nationally representative sample of paediatricians and pediatric subspecialists, detailed data collection, and consideration of the impact of the PANS/PANDAS diagnostic label. Limitations include reliance on retrospective self-report of cases by physicians, and the unusual circumstances of the COVID-19 pandemic, which spanned the study period, and impacted both health and health care. Additionally, it is important to consider the potential for selection bias, particularly concerning the higher proportion of cases reported by physicians in Alberta compared to other provinces. This discrepancy is surprising and does not correspond to the population distribution across Canada.

In conclusion, this study provides important insights into the prevalence, clinical presentation, professional practice patterns, and significant impacts of the PANS/PANDAS diagnostic label on affected Canadian children and their families. The diagnostic uncertainty and discordance between physician assessments and family perceptions of PANS/PANDAS underscore the immense challenges for professionals managing such patients and for families accessing effective care. Given the significant burden associated with these complex neuropsychiatric conditions, it is imperative to better understand their pathophysiology, more clearly delineate these conditions, and ensure the availability of effective multidisciplinary care for these children and their families.

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## POTENTIAL CONFLICT OF INTEREST

AB received honoraria for lectures from the Canadian Pediatrics Review on Infectious Disease. PG has received grants from the following entities: Canadian Institutes of Health Research, PSI Foundation, and SickKids Foundation. He received funding to attend the CIHR Institute of Human Development, Child and Youth Health as a member of the institute's advisory board. TM has received grants from the following entities: the Canadian Institutes of Health Research and the Azrieli Accelerator of the University of Calgary. AY has received grants from the following entities: National Institutes of Health, Canadian Institutes for Health Research, SickKids Foundation, OMS Life, Peterson Foundation, National MS Society, Leong Centre, MS Canada, Stem Cell Network, Centre for Brain and Mental Health, Gary Hurvitz Foundation, Guthy Jackson Foundation, Sumira Foundation, Alexion, Biogen, Hoffman LaRoche, Pipeline. She has received honoraria for lectures and/or participation in grant review panels for Biogen, Ottawa Health Research Institute, American Academy of Neurology, Consortium of MS Centres, MS At the Limits, and BC Health Research. She has received support for attending/speaking at the following meetings; ECTRIMS, ACTRIMS, CMSC, AAN, MSXchange, CNSF, Canadian Pediatric Society, RareKids Can, CANTrain, National MS Society, MS Canada. She has participated on the Data Safety Monitoring Board or Advisory Board for Pipeline Therapeutics. She has had a leadership/fiduciary role in the following committees: IMS Visual, MSARD, Neurology, MS Journal, International Neuroinflammatory Symposium 2023, CNMSC, CANTRAIN, RareKids CAN. MS received grants from the Brain and Mental Health grant, and CPSP/PHAC for the completion of this study. MS received reimbursement for travel expenses from the Department of Pediatrics, Hospital for Sick Children. She also attended the Canadian Paediatric Society Annual Conference Presentation and the Paediatric Update Conference Presentation, for which no charges were made for conference registration for presenters. Additionally, she received support for travel expenses related to two site visits to the CPAE clinic in Tucson, PACE foundation. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

## REFERENCES


1. Swedo SE, Leonard HL, Garvey M, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: Clinical description of the first 50 cases. Am J Psychiatry 1998;155:264–71. doi:10.1176/ajp.155.2.264
2. Swedo S. From research subgroup to clinical syndrome: Modifying the PANDAS criteria to describe PANS (pediatric acute-onset neuropsychiatric syndrome). Pediatr Ther 2012;02:2. https://kids.iocdf.org/wp-content/uploads/sites/6/2015/07/PANDAS-to-PANS-Final-form-for-Pediatrics-Therapeutics-2012.pdf.
3. Murphy TK, Gerardi DM, Parker-Athill EC. The PANDAS controversy: Why (and how) is it still unsettled? Curr Dev Disord Rep 2014;1:236–44. doi:10.1007/s40474-014-0025-3
4. Wilbur C, Bitnun A, Kronenberg S, et al. PANDAS/PANS in childhood: Controversies and evidence. Paediatr Child Health 2019;24:85–91. doi:10.1093/pch/pxy145
5. La Bella S, Scorrano G, Rinaldi M, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS): Myth or reality? The state of the art on a controversial disease. Microorganisms 2023;11:2549. doi:10.3390/microorganisms11102549
6. Gilbert DL. Inflammation in tic disorders and obsessive-compulsive disorder: Are PANS and PANDAS a path forward? J Child Neurol 2019;34:598–611. doi:10.1177/0883073819848635
7. Hutanu A, Reddy LN, Mathew J, Avanthika C, Jhaveri S, Tummala N. Pediatric autoimmune neuropsychiatric disorders associated with group a streptococci: Etiopathology and diagnostic challenges. Cureus 2022;14:e27729. doi:10.7759/cureus.27729
8. Wald ER, Eickhoff J, Flood GE, et al. Estimate of the incidence of PANDAS and PANS in 3 primary care populations. Front Pediatr 2023;11:1170379. doi:10.3389/fped.2023.1170379
9. Leckman JF, King RA, Gilbert DL, et al. Streptococcal upper respiratory tract infections and exacerbations of tic and obsessive-compulsive symptoms: A prospective longitudinal study. J Am Acad Child Adolesc Psychiatry 2011;50:108–18.e3. doi:10.1016/j.jaac.2010.10.011
10. Luo F, Leckman JF, Katsovich L, et al. Prospective longitudinal study of children with tic disorders and/or obsessive-compulsive disorder: Relationship of symptom exacerbations to newly acquired streptococcal infections. Pediatrics 2004;113:e578–85. doi:10.1542/peds.113.6.e578
11. Orlovska S, Vestergaard CH, Bech BH, Nordentoft M, Vestergaard M, Benros ME. Association of streptococcal throat infection with mental disorders: Testing key aspects of the PANDAS hypothesis in a nationwide study. JAMA Psychiatry 2017;74:740–6. doi:10.1001/jamapsychiatry.2017.0995
12. Wang H-C, Lau C-I, Lin C-C, Chang A, Kao C-H. Group A streptococcal infections are associated with increased risk of pediatric neuropsychiatric disorders: A Taiwanese population-based cohort study. J Clin Psychiatry 2016;77:e848–54. doi:10.4088/JCP.14m09728
13. Hesselmark E, Bejerot S. Biomarkers for diagnosis of pediatric acute neuropsychiatric syndrome (PANS)—Sensitivity and specificity of the Cunningham panel. J Neuroimmunol 2017;312:31–7. doi:10.1016/j.jneuroim.2017.09.002
14. Gilbert DL, Mink JW, Singer HS. A pediatric neurology perspective on pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection and pediatric acute-onset neuropsychiatric syndrome. J Pediatr 2018;199:243–51. doi:10.1016/j.jpeds.2018.04.035
15. Allaire J. RStudio: Integrated Development Environment for R, vol. 770. Boston, MA: The R Project for Statistical Computing; 2012:165–71.
16. Government of Canada, Canada S. Census Profile, 2021 Census of Population. https://www12.statcan.gc.ca/census-recensement/2021/dp-pd/prof/index.cfm?Lang=E
17. Aman M, Coelho JS, Lin B, et al. Prevalence of pediatric acute-onset neuropsychiatric syndrome (PANS) in children and adolescents with eating disorders. J Eat Disord 2022;10:194. doi:10.1186/s40337-022-00707-6
18. Singer HS, Giuliano JD, Zimmerman AM, Walkup JT. Infection: A stimulus for tic disorders. Pediatr Neurol 2000;22:380–3. doi:10.1016/s0887-8994(00)00131-4
19. Jaspers-Fayer F, Han SHJ, Chan E, et al. Prevalence of acute-onset subtypes in pediatric obsessive-compulsive disorder. J Child Adolesc Psychopharmacol 2017;27:332–41. doi:10.1089/cap.2016.0031
20. Kilbertus S, Brannan R, Sell E, Doja A. No cases of PANDAS on follow-up of patients referred to a pediatric movement disorders clinic. Front Pediatr 2014;2:104. doi:10.3389/fped.2014.00104
21. Goldstein RB, Olfson M, Wickramaratne PJ, Wolk SI. Use of outpatient mental health services by depressed and anxious children as they grow up. Psychiatr Serv 2006;57:966–75. doi:10.1176/ps.2006.57.7.966
22. Reid GJ, Stewart SL, Barwick M, et al. Predicting patterns of service utilization within children's mental health agencies. BMC Health Serv Res 2019;19:993. doi:10.1186/s12913-019-4842-2
23. Nurminen M. Association of mental health and behavioral disorders with health care and service utilization in children before and after diagnosis. PLoS One 2022;17:e0278198. doi:10.1371/journal.pone.0278198