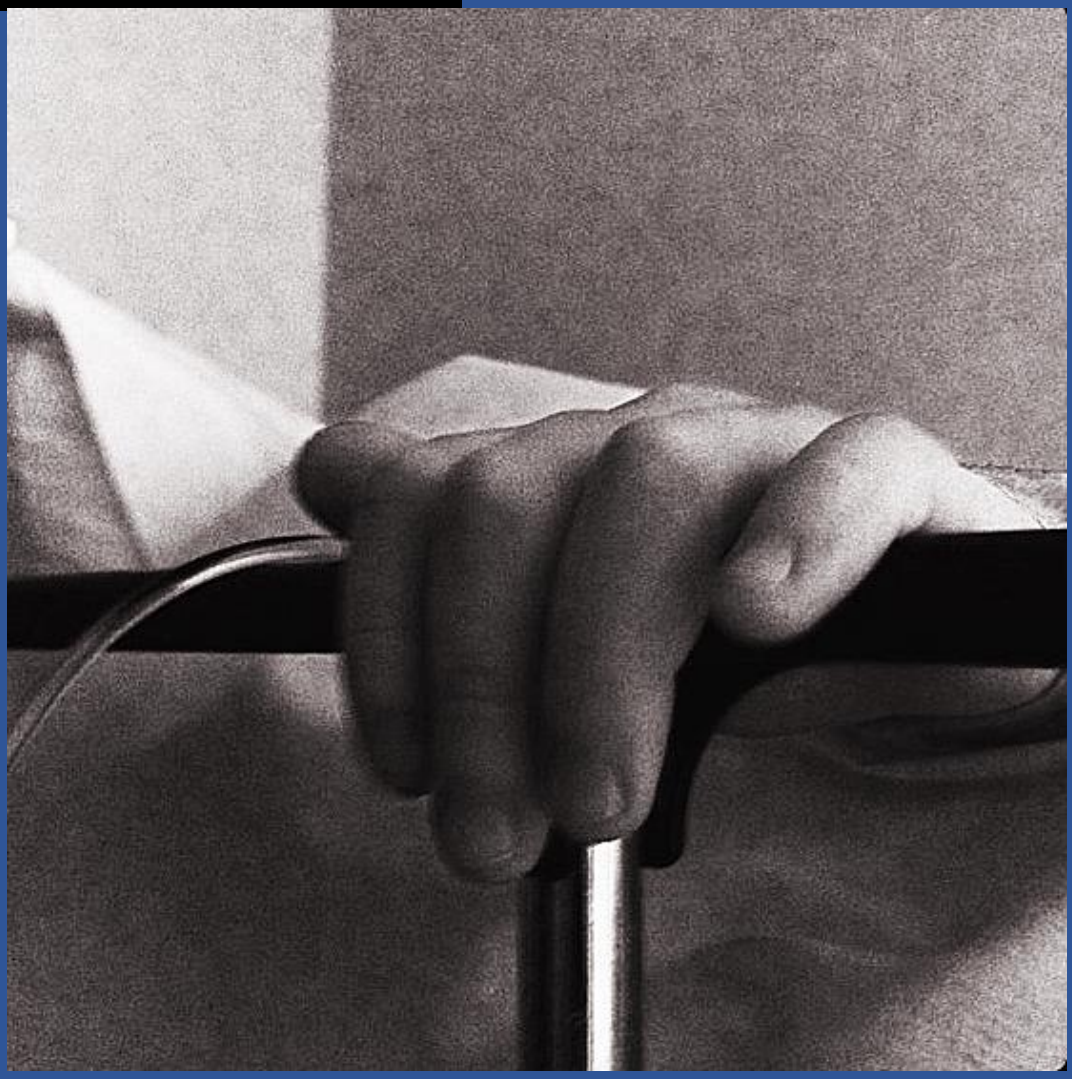
ILLINOIS PANDAS/PANS ADVISORY COUNCIL



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MEMBERSHIP

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- Natalie Lambadjian-Drummond, MD, Whole Child Pediatrics, Yorkville, Ill.
- Wendy Nawara, MSW, BCPA, PANS PANDAS Patient Advocate and Consultant, Naperville, Ill.
- Teresa Schindler, RN, PEL-CSN

- Allison Nickrent, Legislative Liaison, Illinois Department of Public Health, Chicago, Ill.

The Illinois PANDAS/PANS Advisory Council was created in 2015 in accordance with *Public Act 99-0320* to:

- Make recommendations concerning standard practice guidelines for Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections/Pediatric Acute-onset Neuropsychiatric Syndrome (PANDAS/PANS).
- Develop mechanisms to increase clinical awareness of PANDAS/PANS.
- Provide outreach to educators and parents.
- Develop a network of volunteer experts on PANDAS/PANS to serve as resources within the state.

The Illinois Department of Public Health (IDPH) has managed oversight and support of the council since 2015. The priorities of the council in 2021 have been to continue to review the standards of care that medical providers in the state can access, and to educate citizens, health providers, mental health providers, medical students, and education professionals on PANDAS/PANS.

The council consists of physicians, who are board certified in immunology, pediatrics, psychiatry, and family medicine and have expertise and experience in the diagnostics and treatments of pediatric autoimmune neuropsychiatric disorders and/or autism spectrum disorders; other health and mental health care professionals with expertise and experience in the diagnostics and treatments of pediatric autoimmune neuropsychiatric disorders; certified members of the School Health and Special Education divisions of the State Board of Education; representatives of organizations or groups that advocate on behalf of children and families suffering from PANDAS/PANS and/or autism spectrum disorders; legislators; and parents of children who have been diagnosed with PANDAS/PANS.

UNDERSTANDING PANDAS/PANS

For 30 years, PANDAS has been studied extensively at the National Institute of Mental Health (NIMH) and elsewhere across the U.S. and internationally.[3] More recently, a consortium of clinicians, researchers, and scientists has dedicated considerable time and effort to clinical care and study of children with PANDAS and the larger cohort of patients with Pediatric Acute-onset Neuropsychiatric Syndrome (PANS).[2] A medically treatable cause can be found for most cases of PANDAS and PANS. Preliminary data suggest that with appropriate treatment early in the course of illness, and effective use of antibiotics prophylaxis, up to 25-30% of childhood mental illnesses may be able to be prevented.[4]

PANDAS
Pediatric
Autoimmune
Neuropsychiatric
Disorders
Associated with
Streptococcal infections[1]

PANS
Pediatric
Acute-onset
Neuropsychiatric
Syndrome[2]

Evidence exists that demonstrates group A *Streptococcal* (GAS) infections are the causal factor in PANDAS. Antibody studies establish that children with PANDAS have antibodies that invoke bioactivity to produce the acute symptomatology.[5-8] Animal studies show the transference of antibodies from an originally infected mouse to a naïve, healthy mouse to produce the same behavioral abnormalities and obsessive-compulsive disorder (OCD) symptoms.[9-10] This demonstrates that PANDAS/PANS is an immune mediated antibody process. Placebo-controlled trials of antibiotic therapies exhibit significant benefits for both PANDAS and PANS, and trials of prophylactic antibiotics have shown that preventing strep infections leads to reduction or cessation of the neuropsychiatric exacerbations. [11] In mild cases with positive strep cultures, a single course of antibiotics given to eradicate the strep infection can be effective in eliminating the psychiatric and behavioral symptoms. Additionally, a growing body of evidence indicates that PANDAS/PANS are autoimmune encephalitic disorders.[12-13] There are two different types of autoimmune encephalopathies that produced a response to infection with group A *streptococcus* bacteria. One is Sydenham chorea, which is the neurologic manifestation of acute rheumatic fever, while the other is PANDAS.[22] Because intravenous immunoglobulin (IVIG) is widely accepted as a standard treatment for post-infectious autoimmune encephalopathy,[39] when faced with the more moderate to severe presentations of PANDAS/PANS, physicians must rely on immunomodulatory measures, including steroids, intravenous immunoglobulin, and therapeutic plasmapheresis (TPA) to halt this neuroinflammatory process.

Children with PANDAS/PANS who do not receive appropriate treatment remain chronically ill and the progression of the disease may exacerbate symptomatology to the extent that they are unable to attend school, participate in the community, and in some cases may require residential care. In the most severe cases, lack of appropriate medical interventions can result in the progression of clinically associated symptoms, which may result in death due to suicide or complications due to anorexia.

Clinical Presentation

PANDAS and PANS are defined by an unusually abrupt onset of OCD or eating restrictions/anorexia.[1-2]

Comorbidity is present in all children, with most having symptoms in at least four categories[1-2,15]

- Anxiety (particularly separation anxiety)
- Emotional lability and/or depression
- Irritability, aggression, and/or severely oppositional behaviors
- Behavioral (developmental) regression
- Deterioration of school performance
- Sensory or motor abnormalities
- Somatic signs and symptoms, including sleep disturbances, enuresis and urinary frequency

The course of illness is relapsing/remitting, with exacerbations preceded by infections (particularly group A *Streptococcus*) and psychosocial stressors.

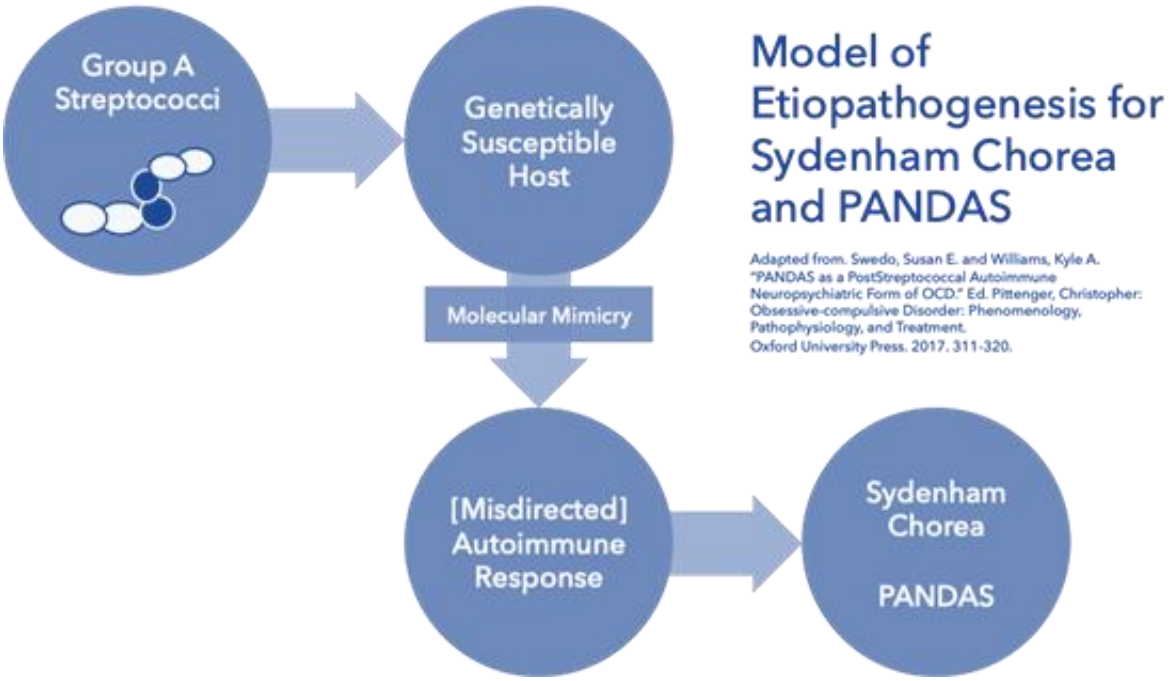
Although early recognition and treatment can eradicate symptoms, children who fail to receive appropriate diagnosis and treatment have increasingly severe episodes, with resultant distress and loss of function (unable to participate in extracurricular activities, stop seeing friends, unable to attend school or even leave a "safe" room in their house). Severe cases often require prolonged psychiatric hospitalizations and may end in death (by suicide, starvation/dehydration, or accidents caused by impulsive behaviors).

Epidemiology/Demographics

- Peak age at onset = 6.5 years[2]
- Boys outnumber girls approximately 2:1[2]
- 1 in 250 children have impairing symptoms (estimates from clinic populations[2,14])
- 5 – 10% of grade-school aged children have observable GAS-related neurologic and behavioral symptoms[14]

Etiology and Disease Mechanisms for PANDAS (Post-streptococcal symptoms)

It is understood that 65-100% of patients with Sydenham chorea have obsessive-compulsive symptoms, with that rate increasing with recurrences.[20] OCD symptoms are often more persistent and difficult to treat than the chorea.[21]



GAS are "molecular mimics" that cause the immune system to produce antibodies that misrecognize host antigens as foreign. This temporary loss of tolerance may become permanent if blood-brain barrier is breached (which GAS exotoxins can do) or if the immune system is repeatedly activated.[22]

Evidence for an etiologic role of GAS (group A *Streptococcus*) infections in PANDAS comes from:

- Clinical observations showing 1:1 correlation between (occult) GAS infections and neuropsychiatric symptom exacerbations.[1,15]
- Epidemiologic studies demonstrating association between GAS infections and choreiform movements, tics, and problem behaviors.[14,23]
- Treatment of GAS infections improves OCD/tic symptoms.[11,16]
- Prevention of GAS infections reduces number and severity of neuropsychiatric symptom exacerbations.[24,25]
- Cross-reactive antibodies present during acute illness, but not during convalescence.[26,27]
- Animal models show that repeated GAS infections in lymphoid tissues, such as tonsils and adenoids, stimulate T-cell production and immune activation in the central nervous system.[10]

Evidence for immune dysfunction in PANDAS comes from:

- Efficacy of immunomodulatory therapies, such as IVIG and plasmapheresis.[17-19]
- Cross-reactive antibodies produce cell signaling, as evidenced by activation of CaM KII.[28,27]
- Animal models have demonstrated that PANDAS sera/antibodies produce neuropsychiatric symptoms, even by passive transfer.[10,28-30]

STANDARD DIAGNOSTIC AND TREATMENT GUIDELINES

The development of the PANS/PANDAS standard diagnostic and treatment guidelines began in 2013 when a group of noted physicians met at the National Institutes of Health to discuss the significant needs of this population of sick children. A diagnostic consensus was developed and subsequently published in the Journal of Child and Adolescent Psychopharmacology in 2015.[41] Follow up treatment guidelines were published in the same journal in July 2017.[37]

The PANDAS/PANS diagnosis is based on subjective criteria and is considered a clinical diagnosis. However, as research has improved, absolute, major, and minor criteria have been developed and can be met in various combinations.[36]

Absolute Criteria

- ☐ Sudden Onset. Sudden and precipitous development of symptoms over the course of hours or even a few days.
- ☐ Characteristic dynamic evolution of nature of symptoms and intensity of symptoms over a period of 2-6 weeks.

Major Criteria

- ☐ Presence of OCD symptoms
- ☐ Separation anxiety (one or both)
  1. Daytime and nighttime dependency on parent's physical presence.
  2. Psychological dependence on familiar physical environment with or without need for parents' presence.
- ☐ Anorexia (one or more)
  1. Acute onset of food and/or liquid refusal
  2. Fear of choking
  3. Fear of vomiting
  4. Inability to swallow because of intolerable smell or texture
  5. Distorted body image (usually in children over 12; and can result from the other types of anorexia)

Minor Criteria Group 1

- ☐ Sleeping disorders (insomnia, night terrors, refusal to sleep alone)
- ☐ Behavior regression (baby talk, temper tantrums, behaviors unbecoming of actual chronological age)
- ☐ Emotional Lability/Depression
- ☐ Hyperactivity, inattentiveness, inability to concentrate (ADHD/ADD diagnosis compatible)
- ☐ Learning disability (particularly mathematics) that was not there prior to symptom onset
- ☐ Hallucinations

Minor Criteria Group 2

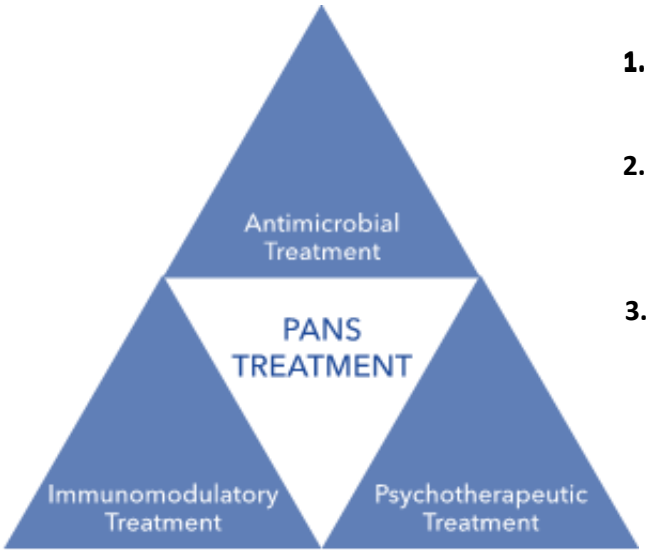
- ☐ "Hyperalert" appearance and/or "puppet-like" facial mannerisms
- ☐ Hypotonia
- ☐ Mydriasis (especially during acute phase of symptoms)
- ☐ Urinary frequency and/or enuresis and/or daytime incontinence
- ☐ Short-term memory loss
- ☐ Increased sensory responses (smells, sounds, light, touch)
- ☐ Fine motor skills deterioration
- ☐ Dysgraphia
- ☐ Tics and/or adventitious movements

Additional Supporting Evidence

- ☐ Positive GAS titers
- ☐ Positive EBV IgM (VCA) (EBNA)
- ☐ Positive ANA titer (speckled)
- ☐ Elevated IgE levels
- ☐ Leukopenia
- ☐ Increased circulating immune complexes (c1q, c3d, Raji cells)
- ☐ Sleep study abnormalities
- ☐ MRI abnormalities
- ☐ EEG abnormalities
- ☐ PET scan abnormalities
- ☐ Positive response to antibiotic trial
- ☐ Positive response to steroid "burst"
- ☐ Other positive specific autoimmune encephalopathic antibodies, such as HSV, VZV, EV, HHV-6, AntiNMDAR, ALE, GAD-65
- ☐ Cunningham Panel (Moleculera Labs)
- ☐ "The best test is still taking a thorough history and listening to the parents," according to Dr. Sue Swedo, Scientist Emeritus, Former Chief Neuroscience Branch, NIMH[42]

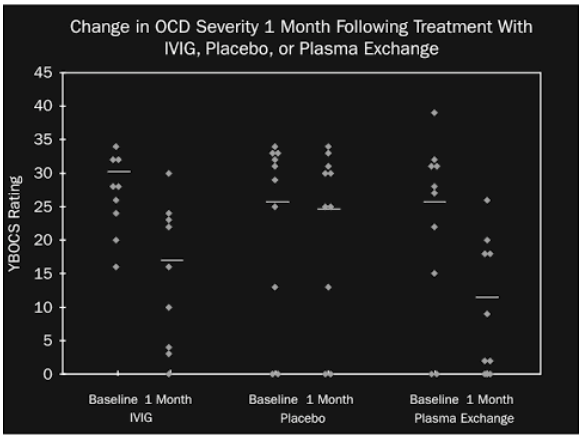
Clinical Management

In 2014, more than 40 physicians and researchers representing the fields of immunology, infectious disease, microbiology, neuroimmunology, neurology, pediatrics, psychiatry, and rheumatology from 23 academic institutions across the U.S., Canada, and Australia convened to craft a standard of care "best practice" guidelines. These evidence-based, peer-reviewed guidelines, published in the Journal of Child and Adolescent Psychopharmacology July/Aug 2017[37], show that there are three recommended complementary treatment modalities when treating cases of PANDAS/PANS:

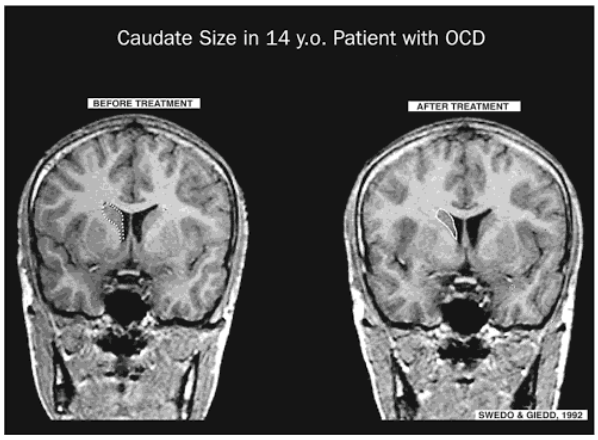


1. Removing the **SOURCE** of the inflammation with antimicrobial interventions.
2. Treating disturbances of the immune **SYSTEM** with immunomodulatory and/or anti-inflammatory therapies.
3. Treating the **SYMPTOMS** with psychoactive medications, psychotherapies (particularly cognitive behavioral therapy), and supportive interventions.[37]

Early recognition and prompt treatment of occult GAS infections can produce complete symptom remission.[16] Antibiotics may help PANS patients, even in the absence of documented GAS infection.[6] Immunomodulatory therapies, such as steroids, IVIG, or therapeutic plasmapheresis, are helpful for severe, debilitating symptoms.[17-19]



A. IVIG vs. Placebo vs. Plasmapheresis
Improvements: 45%, 0% and 58% respectively



B. 20% reduction in caudate size following immunomodulatory treatment

Effects of therapeutic plasmapheresis and intravenous immunoglobulin (IVIG) in PANDAS.
A. IVIG and plasmapheresis produced a significant improvement in OCD severity in children with PANDAS, relative to sham IVIG infusion (from Perlmutter et al., 1999). **B.** Caudate size was reduced by 20% in a child with PANDAS after immunomodulatory treatment (from Giedd et al., 1996).

Additionally, the PANDAS Physicians Network has developed a diagnostic flowchart for physicians to aid in recognition and treatment (https://www.pandasppn.org/flowchart). This chart is updated frequently to reflect most up today knowledge on the condition. Physicians and mental health providers are encouraged to check the site regularly. [38]

Quite often, children with PANDAS/PANS are also identified as having co-occurring conditions including, but not limited to, autism spectrum disorders, immune deficiencies, or other autoimmune illnesses or encephalopathies. In these cases, as in all cases of potential neuroimmune illness, it is very important that treatment decisions are made to ensure the best possible clinical outcome. For example, if a child has both a moderate to severe PANDAS and a documented immune deficiency warranting immunomodulatory treatment, a "loading dose" of immunoglobulin may be required to halt the autoimmune attack before proceeding with the more typical monthly doses prescribed for the immune deficiency.

It is the recommendation of this advisory council that the diagnostic criteria, practice parameters, and treatment protocols identified here shall continue to be practiced as the standard of care for PANDAS/PANS in Illinois. **However, it is imperative that more physicians, educators, and mental health providers become aware of the condition and how to treat it.**

CURRENT 2021 RESEARCH

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PANDAS/PANS BURDEN IN ILLINOIS

Historically, the true incidence of PANDAS/PANS is unknown. The lack of information on incidence is grounded in the fact that current and prior diagnostic coding for PANDAS and PANS result from the lack of a unique diagnostic code specific to these syndromes. Currently, ICD-10 codifies PANDAS under generalized immune disorders (D89.89 Other specified disorders involving the immune mechanism, not elsewhere classified[56]). Although ICD-11 more aptly denotes that PANDAS is an autoimmune CNS disorder (8E4A.0 Paraneoplastic or autoimmune disorders of the central nervous system, brain or spinal cord[57]), a specific code remains absent. Moreover, the dilemmas in coding PANS are similar and more profound. The lack of adequate coding creates not only disagreement on how to classify these syndromes, but also an inability to track the disorder and to compute epidemiological data, and likely results in inadequate reimbursement from insurance claims by health care providers and institutions involved in the care of PANDAS/PANS children. In turn, formulation of diagnostic guidelines and estimation of costs of care become difficult with the paucity of accurate data. It is the opinion of this council that it is imperative for our legislators and insurers to work closely with clinical experts to develop clear and consistent coding, to collect accurate statistics on prevalence, and to analyze health care claims data, in order to standardize and to improve care for these pediatric patients.

Expert members of PANDAS/PANS Collaborative Consortium estimate PANDAS/PANS to affect 1% to 2% of the pediatric population[31], while the non-profit organization PANDAS Network reports the incidence at 1 in 200 children[32]. This is not a small number of children who may be affected by PANDAS/PANS. It is clear that a subset of pediatric mental health problems is the result of and embedded within the population of children diagnosed with PANDAS/PANS. In accordance with the Illinois Mental Health 2013-2018 Strategic Plan, children suffering from PANDAS/PANS meet the definition of having a serious emotional disturbance, which is defined as the "unique needs of children and adolescents under age 18 who have, in the past year, been diagnosed with a mental, emotional, or behavioral disorder resulting in functional impairment that substantially interferes with or limits the child's role or functioning in family, school, or community activities." [34] On a national scale, the CDC reports that 1 in 7 U.S. children between the ages of 2 and 8 years have a mental, behavioral, or developmental disorder. The National Research Council and Institute of Medicine estimate a higher prevalence of up to 20% of U.S. children (1 out of 5) who experience a mental disorder in a given year. Suicide, which can result from the interaction of mental disorders and other factors, was the second leading cause of death among adolescents aged 12–17 years in 2010.[60] When mental health issues persist into adulthood, especially as a result of misdiagnosis or inadequate care, the risk of poor school outcomes, decreased employment, additional health concerns, early mortality, and the cost of caring for people with the disorders is heightened. [33] Without a doubt, pediatric mental health problems are a significant predictor for mental health issues in adulthood and are a substantial public health concern.

A 2016 collaborative study from the PANDAS Network, the University of Buffalo, and the University of South Florida revealed that prompt diagnosis and expeditious treatment of this condition can alleviate symptoms in the short term but can also alter the course of the disease in the long term. "While it is appreciated by a small percentage of clinicians that timely antibiotic intervention and eradication of the inciting infection are integral in the treatment of PANS, this study, for the first time, highlights the importance of such treatment in the long-term clinical picture of PANS. Although PANS is typically recurrent with some chronic features, the data reported herein suggest that early and aggressive treatment of infection may decrease both the likelihood of residual symptoms and the likelihood of recurrence, potentially preventing the high levels of functional impairment seen particularly in the post-

pubertal years. Having increased vigilance for new infections and exposure to GAS is likely also helpful to minimize the impact of recurrence of PANS symptoms," the study concluded.[40] Without appropriate diagnosis and treatment, the illness has the potential to become a chronic life-long condition, requiring extensive and expensive care. There can be no doubt that mental, behavioral, and developmental disorders, such as PANDAS/PANS, and the associated conditions of attention deficit hyperactivity disorder, obsessive compulsive disorder, autism spectrum disorders, and Tourette syndrome have a substantial impact on the health care, families, and communities of Illinois.

In the 2019 census of approximately 2.8 million children under age 18 living in Illinois, the 0.5% low estimation of PANDAS/PANS amounts to approximately 14,000 affected children statewide. Of approximately 150,000 children diagnosed with mental illness in Illinois, due to the under recognition of PANDAS/PANS, a larger subset of these children may actually have pediatric acute onset neuropsychiatric syndrome. Given the treatable medical nature and potential full reversal of neurocognitive deficits in PANDAS affected children, if appropriately diagnosed and treated immediately, the number of children with mental health conditions overall could be reduced, which would substantially limit the burden on the state. As already mentioned, NIMH has estimated 25-30% of childhood mental illness may be preventable through appropriate treatment of PANDAS/PANS.[4] If we compute this estimation with the data suggested by the Illinois Mental Health Strategic Plan[34], in 2013 approximately 43,750-52,500 children and adolescents may have decreased quality of life due to a missed diagnosis of PANDAS/PANS and/or misdiagnosis of serious emotional disturbance.

The financial cost of caring for children with serious mental illnesses (SMI) is profound, and even more so in children with PANDAS/PANS who require concomitant medical, psychiatric, and behavioral treatments. It is estimated the **excess** lifetime cost burden of SMI is $1.85 million per person[58] and that inpatient and outpatient costs amount to $247 billion spent on childhood mental disorders.[53] Hospitalizations due to PANDAS/PANS are significantly more expensive for the Illinois health care system than community-based services. The average length of stay for a child with a psychotic disorder, not otherwise specified (NOS) in Illinois, is 17.9 days[59]. A recent estimate reveals that a five-day psychiatric hospitalization can cost $12,000 in greater Chicago[35]. Currently, the experts on this council recognize that the majority of children with PANDAS/PANS in Illinois experience significant delays, usually several years or more, before receiving adequate diagnosis and treatment. In comparison, the costs of early diagnosis and treatment with generic antibiotics and anti-inflammatories are a significant fraction. The vast economic benefits, in addition to improved medical and social welfare of the affected child and their families, direct this council to stress the urgency for recognition and treatment of PANDAS/PANS at the initial abrupt onset of symptoms.

CONSIDERATIONS DURING THE COVID-19 PANDEMIC

The coronavirus disease 2019 (COVID-19) pandemic has resulted in profound changes in society, from increased attention to infectious disease transmission and medical evolution of a novel infectious agent, to the engagement of public health measures in response to a dire population crisis, and to the personal and collective mental health challenges brought about by normative and often mandated shifts in behavior. There can be no denying that this pandemic has created a watershed moment with long lasting effects on the population into the future. There are a number of social and medical implications of COVID-19 on the PANDAS/PANS cohort that exist, which may similarly affect other groups of children and adults suffering from chronic illness. The council believes that the public's increased interest and understanding of the above factors will result in increased empathy for those suffering with PANDAS/PANS and a renewed drive for education and research in post- and para- infectious neurocognitive disorders.

Increased Mental Health Issues

Prior to the coronavirus pandemic, mental health issues amongst children were increasing. The burden of pediatric mental health disorders is significant, with upwards of 10% of all pediatric hospitalizations attributed to mental health conditions. [53] "An estimated 20% of children and adolescents in the United States meet diagnostic criteria for a mental health disorder. [53] The CDC reports that ADHD, behavior problems, and depression were the most commonly diagnosed mental disorders in children. [44]

- 9.4% of children aged 2-17 have received an ADHD diagnosis. [44]
- 7.4% of children aged 3-17 have a diagnosed behavior problem. [44]
- 7.1% of children aged 3-17 have a diagnosed anxiety disorder. [44]
- 2-3% of children and adolescents have OCD. [45]
- While less prevalent, but nonetheless concerning, collected tic disorder statistics on children are estimated to fall in a .4-.8% range. [46]

Globally, the incidence of mental health issues in children have risen since the start of the COVID-19 pandemic. [48-51] Anxiety, depression, difficulty concentrating, boredom, restlessness, loneliness, irritability, and worrying, are just some of the symptoms being reported. Although the rise of mental health disorders in children may be attributed to a number of factors, including quarantining, school interruption, parental anxiety, uncertainty for the future, and economic instability. A proportion of these presenting disorders may be due to post-infectious complications of a medical disease. A 2018 study reported a significant percentage of pediatric OCD patients meet the requirements for a PANDAS/PANS diagnosis, highlighting the need for screening upon the appearance of initial symptoms. [52] It must be underscored that a variety of mental health disorders are a part of the presenting symptomatology in a PANDAS/PANS diagnosis and should be investigated.

COVID-19 Related PANS

In less than two years' time, a multitude of unexpected and serious medical complications and sequelae of COVID-19 have emerged, including a variety of neurological and neuroinflammatory disorders. The multisystem inflammatory syndrome in children (MIS-C), a complication of pediatric COVID-19 infection has emerged, lending a host of neurological complications thought to arise from central nervous system (CNS) insult, whether from metabolic or hypoxic injury. In addition, the SARS-CoV-2 virus itself, a cytokine storm induced by viral infection, or post-inflammatory antibody response may cause other CNS and neuropsychiatric problems. COVID-19-induced headache, dizziness, delirium, cognitive difficulties, change in mental status, acute cerebrovascular events, mood disorders, acute necrotizing

encephalopathy, meningoencephalitis, and autoimmune encephalopathy have been reported.[47,48] These issues call for increased vigilance in screening and monitoring children for PANDAS/PANS and similar disorders, during and after a COVID-19 infection.

COVID-19 Vaccine Opportunities

COVID-19 vaccines are reducing morbidity and mortality in high-risk groups such as older adults, teens, and children. Additionally, most children and all teens can get COVID-19 vaccination at this time. An estimated 25-50% of the population would need to be immune in order to suppress current rates of community transmission.[61]

Although young children infected with COVID-19 appear to have a milder course and a better prognosis than adults[62], a minority of children have experienced severe courses and have had devastating tolls, including those with MIS-C, mechanical ventilation, and death. Such cases are rare with underlying risk factors for severity which include very young age and co-morbidities, such as immunological conditions (immunodeficiency and immunosuppression), respiratory conditions (asthma, cystic fibrosis), and neurological disability.[63] Similar to other viral pathogens and their vaccines, a natural COVID-19 infection and its ensuant symptomatology may be reduced and potentially prevented by the COVID-19 vaccination. Prevention of natural infection and its complications may be speculated to reduce COVID-19 related PANS as well.

PANDAS/PANS children are known to have immune-dysregulation and a significant proportion have an immunodeficiency status,[54] causing them to be potentially more susceptible to, and vulnerable to complications of, infection. Given this knowledge, the cohort of PANDAS/PANS children who have co-existing immunodeficiency might be considered for prioritization among the pediatric population to receive the COVID-19 vaccine. The complexities of the immune system and its function in each specific child must be considered. For most people who have immunodeficiency, the humoral response to viruses is preserved and most children would still benefit from COVID-19 vaccination. However, for some children with specific immunodeficiencies or who are undergoing immunosuppressive or immunomodulatory treatment, a vaccination may not make sense since the body is unable to mount any effective response to the vaccine or the vaccine might be neutralized by immunomodulatory treatment. In such cases, the vaccine would in essence be wasted on the individual. In certain circumstances of combined immunodeficiencies, live vaccines may result in adverse outcomes.[64] Reports of allergic reactions in certain susceptible individuals have also rarely occurred in early stages of public vaccination efforts, likely to the polyethylene glycol component of the first COVID-19 vaccines available in Western countries.[65] The decision to immunize to COVID-19 the PANDAS/PANS child who has a concomitant immunodeficiency, who is on an immunosuppressive or immunomodulatory treatment, and/or who has allergic predispositions, is best individualized. It is important for parents and caregivers of children with immune problems to defer immunization and first consult with their immunologist. For children with comorbid severe allergies, such as asthma, eczema, or food and drug allergy, a discussion with the treating allergist may be strongly advised.

Further Educational and Health-Related Challenges

Like all children who suffer from chronic diseases, children with PANDAS/PANS and their families are socially and economically vulnerable. They are already at an increased risk for social isolation and have significant educational challenges. Quarantining measures resulting in school closures may further limit the ability of families, particularly families with limited financial resources, to initiate and to maintain mental health counseling, therapeutic and assistive services, and special educational supports, most of

which are school based. The pandemic has also resulted in barriers to adequate health care, including delays in preventative and health maintenance services, appointment scheduling, and diagnostic testing. These barriers are compounded by even more stringent self-imposed isolation measures that families have initiated to protect themselves from increased risks of contracting COVID-19 in order to prevent exacerbating PANDAS/PANS symptoms. Manifestations of these fears and anxieties have been observed to include school refusal, increased separation anxiety, and sleep issues.

As discussed above, PANDAS/PANS children are known to have immune-dysregulation and immunodeficiency,[54] with resultant increased susceptibility to infection and/or their complications. On the other hand, behavioral issues, sensory issues, and anxiety might make common strategies for prevention, such as mask-wearing, usual hygiene practices, and some social distancing methods difficult to perform. Many families might choose to avoid or delay the evaluation of a respiratory illness in their child(ren), either due to fear of catching COVID-19 when attempting to secure medical care, due to insufficient funds, or due to the fear of stigma and consequences of testing positive for COVID-19. These reasons might cause the incidence of PANDAS/PANS to rise, since GAS infections may be missed more often due to less in-person health care being delivered, since GAS may not be sufficiently evaluated under the weight of COVID-19 screening and testing fervor, or since GAS may be empirically treated for general respiratory infection with less effective antimicrobials without sufficient testing. Delays in the rapid evaluation and treatment of GAS with adequate antimicrobials, as well as the use of too-short or ineffective antibiotics, have resulted in the increased risk of GAS-related rheumatic heart disease,[55] and perhaps other immune-mediated GAS complications, such as Sydenham chorea and PANDAS. While there are currently no clear-cut solutions to some of the dilemmas, having an understanding of treatment barriers will facilitate better decision-making among physicians, educators, mental health providers, legislators, insurers, and other stakeholders.

INCREASING CLINICAL AWARENESS

- The Illinois Department of Public Health (IDPH) has created a PANDAS/PANS tab on its website to enable users of their site to learn more about PANDAS/PANS. The tab also provides direct links to the PANDAS Physicians Network flowchart to aid in ease of recognizing the disorder and includes resources for physicians and families. The tab is currently under Child and Maternal Health; however, it may be difficult for health care providers to find. The council recommends that the tab be listed under “Diseases.”
- A 2021 Virtual Summit and Grand Rounds took place April 23, 2021. The Southern Illinois University Department of Psychiatry graciously hosted this event and provided CMEs for health care providers. Plans for subsequent meetings on topics such as Educational Considerations, Insurance and Legislation, and Parental Support are underway.
- The development of presentations that would yield the participants credit for professional education has been investigated. These presentations would be available to members of the council to give upon request. A presentation for schools and teachers has been developed and presented in Naperville, Aurora, and Mokena school districts.
- In collaboration with the Illinois Department of Insurance (IDOI), a document to answer frequently asked questions pertaining to Charlie’s Law and the Autoimmune Encephalitis Coding Law has been developed and was available on the department’s website. A better understanding of navigating the insurance process is needed by the families, as well as the physicians of Illinois. For that reason, the

council recommends that the document be readily available to the public through both the IDOI and the IDPH websites on PANS/PANDAS.

- Encouraged appropriate and consistent access to care for families in need of treatment. Suggested the use of state and national experts when conducting peer-to-peer reviews as other specialists may not yet have sufficient knowledge or experience to offer an informed opinion on physician recommended care.
- The World Health Organization announced June 18, 2018, its preparations for the ICD-11 (International Classifications of Diseases) to be implemented in 2021. Having a code for PANDAS would allow better access to insurance covered care for all families in the state as it describes PANDAS as an autoimmune encephalopathy. The diagnostic code is 8E4A.0
- The council supports Charlie's Law, *P.A. 100-0024*, that was signed into effect July 18, 2017. This law should have enabled children in Illinois to access insurance covered care for treatments of PANDAS/PANS. Because families continue to be met with roadblocks from insurers regarding this law, members of the advisory council supported efforts of legislators to introduce subsequent clarifying bills that would make it easier for families and physicians to gain access to treatments covered by insurance. Legislation for 2022 is currently under consideration.
- The council supports the Autoimmune Encephalitis Coding Public Act, P.A. 101-0448, that was signed into law August 23, 2019. For billing and diagnosis purposes, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections and pediatric acute onset neuropsychiatric syndrome shall be coded as autoimmune encephalitis until the American Medical Association and the Centers for Medicare and Medicaid Services create and assign a specific code for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections and pediatric acute onset neuropsychiatric syndrome. Provides that thereafter, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections and pediatric acute onset neuropsychiatric syndrome may be coded as autoimmune encephalitis, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, or pediatric acute onset neuropsychiatric syndrome.
- Council advocacy for future legislation as it pertains to meeting the needs of PANDAS/PANS families will be ongoing.
- The council recommends two excellent learning opportunities for health care providers in 2022. The Inflammatory Brain Disorders Conference takes place online May 21-22, 2022. For more information see https://neuroimmune.org/inflammatory-brain-disorders-conference-2022/. Also, Understanding the Spectrum of Childhood Encephalitides Including PANDAS and PANS will occur February 22, 2022. More information can be found at https://pandasnetwork.org/wp-content/uploads/2021/12/Final-Brochure-Text-Draft_Encephalitis-Brochure_11.1.21.docx.pdf.

NETWORK OF EXPERTS

Throughout the country there are many physicians practicing in the relevant clinical areas pertaining to the diagnostics and treatment of PANDAS/PANS. In addition, there are scientists continually researching the condition to improve upon the care of children. The PANDAS/PANS Collaborative Consortium members are listed here:

- **Harvard University (Massachusetts General Hospital)** – Kyle Williams and Dan Geller (Child Psychiatry), Mark Pasternack (Pediatric Infectious Diseases)
- **Yale University** – James Leckman, Robert King (both Child Psychiatry)
- **Columbia University** – Dritan Agalliu (Basic Science of blood-brain barrier), Tyler Cutforth (Basic Science), Wendy Vargas (Neurology), Shannon Delaney (Child Psychiatry, Lyme disease)
- **Nemours/Delaware Children's Hospital** – Jo Elia (Child Psychiatry), Harry Chugani (PET neuroimaging)
- **NIMH** – Susan Swedo (Scientist Emerita, Pediatrics)
- **Georgetown University** – Beth Latimer (Pediatric Neurologist), Earl Harley (ENT), Heidi Appel (Pediatrics)
- **University of South Florida** – Tanya Murphy (Child Psychiatry), Jolan Walter (Immunology)
- **Loyola University** – Miro Kovacevic (Pediatrics)
- **University of Minnesota** – Pat Cleary (basic science, microbiology of GAS), Gail Bernstein (Psychiatry)
- **Baylor University** – Eyal Muscal (Pediatric Rheumatology)
- **University of Oklahoma** – Madeleine Cunningham (GAS microbiology; immune response to infection)
- **University of Arizona** – Sydney Rice (Developmental-Behavioral Pediatrics), Michael Daines (Pediatric Immunology), Chris Speakerman (Nurse Practitioner)
- **Stanford University** – Jenny Frankovich (Peds Rheumatology), Margo Thienemann (Child Psychiatry)
- **Moleculera Labs** - Craig Shimasaki (Antibody Testing)
- **PANDAS Physicians Network** – David Brick (Pediatric Cardiology)
- **University of California San Diego** - Jay Giedd (Pediatrics)
- **Virginia Commonwealth University/ VCU Medical Center** - Wei Zhao (Immunology), David Jaffe (Neurology)
- **Miami Children's Hospital** - Reuven Bromberg (Rheumatology), Ann Hyslop (Neurology)

The PACE Foundation has led the way in creating multidisciplinary clinics that are on the leading edge of patient care, contributions to research, and the acceleration of science. Clinics can be accessed at nine medical universities throughout the U.S.

- University of Arizona-CPAE Center of Excellence peds.arizona.edu/cpae
- Banner Children's at Desert (Arizona) - CPAE Clinic bannerhealth.com
- University of Arkansas Children's Hospital - CPAE Center uamshealth.com/location/cpae-clinic
- Dartmouth University PANS Clinic chadkids.org
- Greater Regional Health Center – Iowa CPAE/PANS Clinic greaterregional.org/cpae
- University of Wisconsin PANS Clinic uwhealth.org/findadoctor/clinic/1292
- Stanford University Affiliated PANS Clinic med.stanford.edu/pans
- Harvard University Pediatric Neuropsychiatry & Immunology Clinic massgeneral.org/children/pediatric-neuropsychiatry-and-immunology/
- University of California Los Angeles Affiliated PANS Clinic semel.ucla.edu/catp

Within Illinois, the practicing past and present members of this advisory council can be consulted for their expertise in the appropriate areas.

- Gloria Barrera, MSN, RN, PEL-CSN, RN Course Facilitator, Illinois State Board of Education
- Teresa Schindler, RN, PEL-CSN
- Pamela Campbell, MD, Child Psychiatry, Southern Illinois University
- Anette Mnabhi, DO, Synergy Healthcare
- Wendy Nawara, MSW, BCPA, PANS Patient Advocate and Consultant
- Greg Sharon, MD, Immunologist, Asthma and Allergy Center
- Anjum Usman-Singh, MD, True Health Medical Center
- Dareen Siri, MD, FAAAAI, FACAAI, Midwest Allergy Sinus Asthma, SC

- Ardyth Holbrook, LCSW, Edward-Elmhurst Hospital

OUTREACH

- The professional members of the advisory council are available as a speakers' bureau.
- The council has developed a list of medical associations, education associations, and medical schools throughout Illinois that can be targeted to receive general information on the diagnosis and treatments of PANDAS/PANS.
- The council has exhibited locally at the Illinois Chapter of the American Academy of Pediatrics conferences.

RECOMMENDATIONS FOR THE FUTURE

In keeping with the original goals of *P. A. 99-0320*, while also expanding upon our goals for 2022, the PANDAS/PANS Advisory Council makes the following recommendations:

Enact Standard Practice Guidelines

Because the National Institute of Mental Health division of the National Institute of Health, the PANDAS/PANS Collaborative Consortium, and the PANDAS Physicians Network have established diagnostic and treatment guidelines that have been published and are now being employed by numerous experts and relevant practicing physicians throughout the country, the PANDAS/PANS Advisory Council of Illinois is recommending the standardization of care as reported here. The advisory council recognizes that medicine is an ever changing and evolving field, and as such, it also recommends the members of this council stay up to date on any new science, research, and protocols to advise as needed.

Develop Mechanisms to Increase Public Awareness

- With IDPH, Illinois Department of Human Services, and other pertinent government agencies, assist in the creation of awareness campaign materials appropriate for doctors' offices and public health clinics.
- Request assistance from Illinois State Medical Society, the Illinois American Academy of Pediatrics, and other professional societies to disseminate educational materials.
- Encourage any appropriate state agencies to provide an educational tab about PANDAS/PANS on their respective websites, or link to the IDPH tab, as well as local resources (treating physicians, support organizations).
- With local group PANDAS/PANS Advocacy and Support of Illinois and assistance from the PANDAS/PANS Clinical Research Consortium, participate in the development of CEU/CME online training for pediatricians, mental health providers, and first responders/emergency departments.
- Investigate the possibility of bringing a PANDAS/PANS Center of Excellence to an Illinois teaching hospital to facilitate prompt recognition and treatment of PANDAS/PANS to ease the burden on the state.
- Increase PANDAS/PANS educational opportunities in 2022. Consider more than one remote learning opportunity to expand understanding. Meetings will pull together individuals from the various specialty areas involved with children and families impacted by PANDAS/PANS and will continue to develop solutions for them. Education on the published treatment guidelines, new science, and the development of treatment resources should address the ongoing challenges of educating health care providers, educational professionals, and families about PANDAS/PANS.

- Develop a flowchart, with the assistance of the Illinois Department of Insurance and the Illinois Department of Labor, for families and doctors to navigate the insurance process more easily.
- Invite a member of the Illinois Chapter of the American Academy of Pediatrics and a member of the Illinois State Medical Society to attend advisory council meetings.
- Investigate the inclusion of coverage of PANDAS/PANS treatment in Medicaid managed care plans.

Provide Outreach to Educators and Parents

- With IDPH, Illinois Department of Human Services, Illinois State Board of Education, and other pertinent government agencies, assist in the creation of awareness campaign materials appropriate for school nurses, school social workers, school psychologists, and school administrators.
- Continue to encourage the use of strep notices, and written explanations of school policies regarding the reporting of classroom illnesses and healthy practices to avoid the spreading of disease. Consider basic information on PANS/PANDAS to be added to parent handbooks.
- Increase understanding of available support organizations for families through participation in state agencies' special events, such as the IDPH's School Health Days.
- Provide professional development for teachers and administrators.
- Encourage the utilization of the Illinois Department of Insurance to regulate insurance companies and to protect consumers through assistance and the provision of information about the insurance process.
- Promote the use of the Office of the Illinois Attorney General's Healthcare Bureau to handle issues pertaining to consumer issues on health care accessibility.

Increase Understanding of The Burden on Illinois

- Request IDPH and IDOI gather data and surveillance of incidence statistics on PANDAS/PANS and its co-occurring conditions, such as autism spectrum disorder, immune deficiencies, or other autoimmune conditions in children.
- Encourage Public Health-Directed Means to Prevent and Treat PANDAS/PANS
  Prior to the COVID-19 pandemic, researchers worldwide were prioritizing the development of a cost-effective group A Streptococcus vaccine that reduces pharyngitis and tonsillitis.[66,67] With marked advances in vaccine technology and coordinated global sharing of information and efforts, a GAS vaccine might evolve more quickly than previously imagined. With world-class academic, industry, and pharmaceutical institutions in Illinois, GAS vaccine research could be incentivized in the post-COVID-19 era.
  GAS infections are currently tracked by IDPH. Along with IDPH and Illinois public schools, a coordinated public health and school-based initiative to encourage identification and full-course antibiotic treatment for GAS, including information on potential complications of inadequately treated GAS infections, and information on PANDAS/PANS, would be impactful from a primary and secondary public health standpoint.

The PANDAS/PANS Advisory Council will continue to work on its commission to review recommendations concerning standard practice guidelines for PANDAS/PANS, to develop mechanisms to increase clinical awareness of PANDAS/PANS, to provide outreach to educators and parents, and to develop a network of volunteer experts who can serve as resources within the state.

Advisory council meetings in 2022 will be held bi-monthly via WebEx on the third Tuesday of the relevant month at 9 a.m. Central Time. Call-in numbers are also available. Tentative dates include

January 18, March 15, May 17, July 19, September 20, and November 15, 2022. For more information, or if there is interest in joining the council, contact Allison Nickrent at Allison.Nickrent@Illinois.gov.

In closing, PANDAS/PANS has long been a misunderstood condition. However, when it is estimated to effect approximately 1 in 200 children, its potential detriment cannot be ignored. The present available scientific evidence provides an excellent framework for the state of Illinois to impact the positive outcomes for these children and to reduce the potential long-term physical and mental health consequences they may suffer.

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