Dear PACE Foundation Team,

I am writing to ensure that you have an accurate picture of the true prevalence and incidence of Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) and Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS).

While our early clinic-based estimates suggested that PANDAS was an uncommon condition affecting 1 in 200 grade-school aged children, recent epidemiologic research suggests that PANS is actually much less frequent, affecting less than 1 in 11,700 children. (Wald et al 2023). The more recent data are consistent with PANS and its subtype, PANDAS, being "rare" disorders that are deserving of orphan drug designation for future clinical trials.

Given the inconsistencies in prior frequency estimates, and ongoing misrepresentations of PANS (and PANDAS) prevalence, I am writing this letter to summarize the known facts and address areas of discrepancy.

Background and Early Prevalence Estimates

The first frequency estimates were derived for PANDAS on the basis of epidemiologic field studies of OCD and observations made in our clinic at NIMH which was dedicated to research and treatment of childhood-onset obsessive compulsive disorder (OCD). The epidemiologic survey and follow-up interviews revealed that OCD affects approximately 1% of children and adolescents, and as many as 2% of young adults. Younger onset patients were noted to have a unique clinical presentation characterized by a 2:1 male:female ratio and increased frequency of co-occurring tics, ADHD and other neurologic signs and symptoms. More than 50% of the early-onset cases had a history of an abrupt onset of OCD accompanied by multiple co-occurring symptoms (as defines PANS), as well as choreiform movements observable on systematic neurologic examination. These observations were confirmed in a second OCD specialty clinic (T. Murphy, Univ FL-Gainesville). By extrapolating our observations onto the larger cohort of OCD patients, we derived the 1 in 200 frequency estimate. However, that estimate appears to have been artificially inflated by environmental factors unique to the DC Metro and central Florida regions – both of which were noted to have an unusually high prevalence of "rheumatogenic" strains of Group A streptococci and thus, a disproportionately high incidence of post-streptococcal sequelae, including PANDAS. Therefore, we usually cited the "guess-timated" frequency of PANDAS and PANS as 1 in 200 to 1 in 500.

Advocacy groups, such as the PANDAS Network, advertised only the 1 in 200 figure and it quickly became the accepted prevalence rate, despite having no basis in systematically collected data. To complicate matters further, a 2017 American Academy of Pediatrics Newsletter erroneously quoted me as saying that approximately 1% of grade-school-aged

children have PANS/PANDAS (Pupillo, 2017). In fact, the 1% estimate refers to the frequency of acute-onset neuropsychiatric symptoms, including subclinical obsessivecompulsive symptoms, tics, and ADHD-like behaviors, without regard to clinical impairment or consideration of whether or not the symptoms meet PANS or PANDAS. Our experience with screenings for a NIMH-Yale clinical trial of PANS show that such cases are far fewer than the number of children with some post-infectious neuropsychiatric symptomatology as we had to screen over 1200 potential cases to secure 50 who met PANS or PANDAS criteria and had symptoms severe enough to warrant treatment in the trial. (K Williams et al. AJP)

Contemporary Epidemiological Evidence

Three recent studies have provided the methodological rigor necessary to estimate prevalence and incidence more accurately (Jaspers-Fayer et al., 2017; Wald et al., 2023; Goren et al., 2024). These recent studies employed strict diagnostic criteria and systematic case review, and all three concluded that PANS/PANDAS is rare.

- Jaspers-Fayer et al. (2017) conducted a cross-sectional evaluation of 136 pediatric patients receiving treatment for OCD in Canada. Seven patients (5%) fully met criteria for PANS/PANDAS, corresponding to an estimated frequency of 0.05–0.1%. Extrapolated to the U.S. population, this equates to approximately 35,000–70,000 individuals—well below the 200,000 threshold commonly used to define rare diseases.

- Wald et al. (2023), presented the most robust incidence estimate to date and was based on a retrospective review of 95,498 medical records from children aged 3–12 years receiving care between 2017 and 2019 at three large U.S. academic medical centers. Using pre-specified criteria and independent dual-review, 357 potential cases were identified, of which only 13 met full diagnostic criteria for PANS or PANDAS. The pooled annual incidence across study sites was 8.5 cases per 100,000 children (95% CI: 5–15), corresponding to approximately 1 in 11,765 children. The mean age of onset was 7.1 years, with a male predominance, consistent with prior clinical observations. Applying this incidence rate to the current U.S. pediatric population (approximately 70.6 million youth aged 3–19 years) yields an estimated 5,998 newly diagnosed cases per year.

- Goren et al. (2024) presented national data from Canada further supporting the rarity of PANS/PANDAS. Using the Canadian Paediatric Surveillance Program, the study identified cases reported by pediatricians over a two-year period and estimated a prevalence of approximately 1 in 60,155 children (0.0017%).

Cumulative Prevalence Considerations

Diagnostic criteria for PANDAS require prepubertal onset, and PANS criteria specify childhood onset; therefore, the at-risk population is limited to pediatric age groups. Clinical data further suggest that most cases begin between ages 3 and 12, and that illness duration is typically less than three years (Leon et al., 2018).

Even using a liberal estimate that includes all individuals aged 3–19 years, cumulative prevalence would be approximately 95,968 individuals in the United States. This figure remains well below the threshold defining rare or orphan diseases (<200,000).

Conclusion

In summary, early prevalence estimates were based on indirect extrapolations and clinical observations rather than epidemiologic measurements. These estimates have been replaced by population-based investigations which revealed that PANS is a rare pediatric disorder, affecting fewer than 1 in 11,700 children annually.

The rarity of the PANS and PANDAS should not detract from our zeal in finding effective intervention and prevention strategies. Affected children suffer terribly and their families suffer along with them – physically, emotionally, financially and in every other aspect of daily life. The toll is tremendous and demands our best efforts to increase awareness, invest in life-saving research and deliver appropriate care. It is my hope that clarifying that PANS and PANDAS are "rare" disorders will facilitate those efforts.

Sincerely yours,

Susan E. Swedo. M.D.

Supported by Leading U.S. National Multi-Discipline PANS Centers of Excellence and Clinics

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