In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 13-591V

(to be published)

GREG PALATTAO *and* ANGELA PALATTAO, *as Parents and Natural Guardians of minor*, R.P.,	*	
Petitioners,	*	Filed: February 4, 2019
v.	*	
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Decision; Entitlement; Dismissal of Claim; Transverse Myelitis ("TM"); *Althen* Prong Three; Innate Immune System Activation
Respondent.	*	

Kate Gerayne Westad, Larkin Hoffman, et al., Ltd., Minneapolis, MN, for Petitioners.

Mollie D. Gorney, U.S. Dep't of Justice, Washington, DC, for Respondent.

DECISION DENYING ENTITLEMENT[1]

On August 20, 2013, Greg and Angela Palattao filed a petition on behalf of their minor child, R.P., seeking compensation under the National Vaccine Injury Compensation Program (the "Vaccine Program").[2] Petitioners allege that R.P. suffered from transverse myelitis ("TM") as a result of receiving his third round of childhood vaccinations (including diphtheria-tetanus-acellular pertussis ("DTaP"), haemophilus influenza B ("Hib"), inactivate polio virus ("IPV"), pneumococcal conjugate ("PCV"), and his first dose of the influenza vaccine) on January 7, 2013.

[1] This Decision will be posted on the United States Court of Federal Claims website, and in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 (2012). **This means the Decision will be available to anyone with access to the internet**. As provided by 42 U.S.C. § 300aa-12(d)(4)(B), however, the parties may object to the published Decision's inclusion of certain kinds of confidential information. Specifically, under Vaccine Rule 18(b), each party has fourteen days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, the whole Decision will be available to the public in its current form. *Id.*

[2] The National Vaccine Injury Compensation Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755 (codified as amended at 42 U.S.C. § 300aa-10 through 34 (2012)) [hereinafter "Vaccine Act" or "the Act"]. Individual section references hereafter will be to § 300aa of the Act.

Petition ("Pet.") (ECF No. 1). An entitlement hearing was held on May 17-18, 2018, followed by a half-day rebuttal hearing on August 20, 2018. The parties thereafter filed post-hearing briefs on October 29, 2018. ECF Nos. 90-91.

After considering the record as a whole and the testimony at hearing, I find that Petitioners have failed to carry their burden establishing causation, and therefore their request for compensation under the Vaccine Program must be denied. While Petitioners made a number of persuasive points regarding the role of certain immune system components in causing TM, there is insufficient reliable evidence to support the conclusion that the vaccines he received are *themselves* reasonable explanations for it, or (even more importantly) that they could cause TM in the short timeframe in which his symptoms first presented.

I. Factual Background

R.P.'s Birth and Early Medical History

R.P. was born to the Palattaos on July 6, 2012, at 39 3/7 weeks gestation, via spontaneous vaginal delivery after an uncomplicated pregnancy. Ex. 8 at 1. Mrs. Palattao's medical records reveal, however, that she experienced recurrent urinary tract infections, material renal calculi, and depression during the pregnancy, for which she was prescribed antibiotics and Prozac. *See, e.g.*, Ex. 3 at 1-3; Ex. 8 at 1. R.P.'s Apgar scores at birth were 8 and 9 at one minute and five minutes. Ex. 8 at 2. Apart from a reported concern for respiratory distress (which appeared to resolve on its own), R.P.'s newborn exam was normal. *Id.* at 3-8.

According to his treating pediatrician, Dr. Lian Tio of Health Partners in Minneapolis, Minnesota, R.P. was essentially healthy and developing normally during his first two months of life. Ex. 8 at 15-30. The Palattaos voiced no concerns about his behavior or development at birth, and his first well-baby examination was normal (apart from newborn acne/jaundice on the face). *Id.* at 16. At his two-month well-baby visit, R.P. was noted to be feeding every 2-3 hours and stooling 2-5 times per day. *Id.* at 19. His neurologic exam was normal and he was assessed as an overall "healthy infant." *Id.* at 20.

R.P. returned to see Dr. Tio on September 10, 2012, for his two-month well-baby examination. Ex. 8 at 19. He received his first round of childhood vaccinations (including DTaP, Hib, PCV, IPV, and rotavirus), along with a second Hep B vaccination. *Id.* at 24-45. No adverse effects were reported. *Id.* Thereafter, R.P. presented for his fourth-month well-baby examination on November 12, 2012, and received a second round of childhood vaccinations, along with a third Hep B vaccination. *Id.* at 26-27. Again, no adverse events were noted. *Id.*

On December 21, 2012, R.P. (now five months old) and his father returned to see Dr. Tio, reporting that R.P. had been suffering from cold and cough symptoms for three weeks. Ex. 8 at 31. R.P. was afebrile, but had been crying that week for "no reason." *Id.* R.P.'s father explained that the family planned to travel out of town for the Christmas holiday. *Id.* Dr. Tio assessed R.P. with an "occasional deep sounding cough," but on examination determined that his lungs were clear and that he was alert. *Id.* The assessment also noted "wax on both ear canal[s]" that could be removed with a curette. *Id.* Dr. Tio diagnosed R.P. with a "prolonged" upper respiratory infection and "right serous otitis media," and prescribed Amoxicillin. *Id.* He recommended that R.P. return to the clinic in six months for a follow-up. *Id.*

January 2017 Vaccinations and Subsequent Medical Problems

On the morning of January 7, 2013 (seventeen days later), R.P. presented to Dr. Tio for his six-month well-baby visit. His December 2012 illnesses appeared to have resolved by this point in time. Ex. 8 at 33-35. Exam notes indicated that R.P. was able to roll from his back to his stomach, and could transfer objects from one hand to the other. *Id.* R.P.'s physical and developmental exam were normal, and the Palattaos voiced no concerns. *Id.* Exam notes make no mention of any further ear complaints or URI symptoms. *Id.* R.P. received his third round of childhood vaccinations (including DTaP, Hib, PCV, and IPV), as well his first seasonal influenza vaccination. *Id.* at 24-25, 31.

Mrs. Palattao called Dr. Tio's office on January 8, 2013 (one day post-vaccination) around 5:30 PM to report that R.P. had a fever of 101.6 degrees. Ex. 8 at 39. Mrs. Palattao also reported that she had picked him up from daycare and noticed he was experiencing dyspnea, limpness, weak crying, and weakness. *Id.*; *see also* Ex. 8 at 40 ("pt's mother states that since 17:00 pt is unable to sit up by himself or hold up his head, he has labored breathing"), 40 ("when he cries he does not make any noise, and has shortness of breath"). The nurse advised R.P.'s mother to take him to the emergency room immediately. *Id.* The telephone note also indicated that R.P. had fed somewhat less than usual (10 ounces instead of 16) that day, and that he was experiencing URI symptoms (i.e. rapid respirations) and irritability. *Id.* at 39.

That evening the Palattaos took R.P. to Children's Hospitals and Clinics of Minnesota ("Minneapolis Children's"). Ex. 8 at 41; Ex. 5 at 1-2. Upon admission, he was examined by ER physician Dr. Patrick Carolan. Ex. 5 at 1. The chief complaint was noted to be fever (starting during the day at daycare) and "decreased activity." *Id.* Dr. Carolan noted that R.P. had received a round of childhood vaccinations the previous day, and had also recently completed a ten-day course of oral antibiotics for "fluid behind the eardrums" and a URI. *Id.* The ER history note further indicated that R.P. had fed well during the morning hours on January 8th, but was running fevers, and by mid-afternoon "seemed much less active overall," along with noticeable behavioral changes. *Id.* In addition, the record states that "[h]e has had no urinary output per day care report

relayed to mother." *Id.* This record thus seems to suggest that the Palattaos were informed by the daycare about R.P.'s progression that day.

Upon exam, Dr. Carolan noted that R.P. was slightly congested with a temperature of 98 degrees. Ex. 5 at 1. He appeared to have normal movement in his extremities. *Id.* Respirations appeared unlabored. *Id.* at 2. His neurological exam revealed "normal tone and power." *Id.* A chest x-ray also revealed normal imaging, and R.P.'s breathing improved over the course of a few hours. *Id.* Following a well-feeding, Mrs. Palattao reported that R.P. was interacting and breathing more normally (as opposed to earlier that evening). *Id.* He was released home and the Palattaos were encouraged to monitor R.P. for infection and follow up if his symptoms progressed. *Id.* Upon discharge, Dr. Carolan opined that R.P.'s fever and "transiently altered behavior" were likely both related to the vaccines he had received the day before. *Id.*

R.P.'s symptoms worsened over the next 24 hours. Ex. 5 at 10-11. His parents therefore brought him back to the ER the next day, on January 9, 2013. *Id.* at 10. Mrs. Palattao reported to Dr. Micah Niermann, an internist, that R.P. had been well prior to receiving his six-month-old vaccinations on January 7, 2013 (at approximately 8:00 AM). *Id.* She estimated that around 3:00 AM on the following Tuesday (January 8, 2013), however, R.P. became more fussy and irritable, and did not feed well. *Id.* It also appears Mrs. Palattao reported a fever with onset *prior* to his arrival at day care, although that is inconsistent from the ER record from the immediately prior date. *Id.* ("did have temperature up to 101.5 that morning, but was still doing well and went to day care"). She otherwise noted that R.P. had appeared well enough when she dropped him off at daycare, but appeared to have "lower tone" and weakness when she picked him up around 5:00 PM that evening, which prompted the initial ER visit. *Id.* at 10. Mrs. Palattao also reported that since the ER visit the prior evening, R.P. had continued to weaken. *Id.* He had an episode during the morning hours where he "gasped for air" and "seemed to stop breathing for 5 to 10 seconds and turned blue around the lips." *Id.* Some vomiting followed, and it was noted R.P.'s temperature was 100.5 (but had normalized as the day progressed). *Id.*

Upon admission, R.P. was examined by Dr. Niermann. Ex. 5 at 10. Dr. Niermann observed R.P. to be "floppy in his mother's arms" with minimal, if any, movement in his extremities. *Id.* He was unable to sit on his own and had poor head control. *Id.* Exam notes revealed low muscle tone and strength, diminished tendon reflexes, and trouble breathing ("belly breathing"). *Id.* at 11. Due to his rapid decline in health, R.P. was admitted and transferred to the pediatric intensive care unit ("PICU") for further evaluation. *Id.* In the PICU, R.P. was evaluated by Dr. John Fugate (an intensivist). *Id.* at 13-24. Upon exam, Dr. Fugate similarly noted that R.P. was experiencing weakness/limpness "significant" difficulty breathing, decreased deep tendon reflexes, and a distended abdomen. *Id.* at 14. Differential diagnoses included Guillain-Barré syndrome, botulism, infection, intracerebral or intraspinal event, possible post-polio syndrome, and myasthenia gravis.

Id. at 11, 14-15. Shortly after admission, R.P. was intubated and a central line was placed. *Id.* at 15.

During his hospitalization, R.P. underwent a comprehensive work-up, including an MRI of his spinal cord that showed extensive signal abnormalities in his cervical and thoracic cords (consistent with a diagnosis of TM). Ex. 5 at 17. The MRI was negative for demyelinating disease. *Id.* at 16. A lumbar puncture and cerebrospinal fluid ("CSF") analysis revealed a 173 white blood cell count (with 87 percent neutrophils and 21 percent lymphocytes), elevated protein at 87, but unremarkable glucose. *Id.* at 21-22. Cultures for viruses and bacteria were negative. Traditional blood tests for inflammation (including sedimentation rate) were similarly negative, though one such test, the CRP rate, was noted to be "quite low" (at 0.5). *Id.* at 20.

Thereafter, a specialist in infectious disease, Dr. Tamara Pozos, was consulted on January 10, 2013, to rule out any potential infectious etiologies. Ex. 5 at 18. Dr. Pozos opined, based on her review of R.P.'s medical history, imaging studies, and lab work at the time, that R.P. likely had TM "secondary to a viral process that he was able to clear in late December with consequent immunologic myelitis." *Id.* at 23. An infectious disease panel, including bacterial cultures from R.P.'s blood and CSF, was negative, however. *Id.* at 24. With regard to R.P.'s recent vaccinations, Dr. Pozos noted that the "live attenuated" flu vaccine had been associated with TM, though she disputed that an inactivated flu vaccine of the kind R.P. received[3] could trigger such an injury (due in part to the extremely short interval between vaccination and onset of R.P.'s symptoms). *Id.*

R.P. was also evaluated by a neurologist, Dr. Abigail Boetticher, during this hospital stay (on January 10, 2013). Ex. 5 at 25-26. R.P.'s health history recorded during this visit included references to both his URI in December 2012, as well as his receipt of his six-month vaccinations (including the flu vaccine) "[one] day before onset." *Id.* at 26. Dr. Boetticher reported that R.P. presented with "rapidly progressive weakness and decreased muscle tone over the past 2 days" (placing onset on January 8, 2013). *Id.* at 25. Dr. Boetticher diagnosed R.P. with TM with accompanying respiratory failure. *Id.* at 26.

While in the hospital, R.P. was treated with high doses of a corticosteroid for five days but showed no significant improvement to his paraplegia. Ex. 5 at 37. On January 13-14, 2013, a second neurologist, Dr. Lawrence Burstein, examined R.P. and assessed him with TM, recommending that his treatment be adjusted to include IVIG therapy followed by plasmapheresis. *Id.* Dr. Burstein opined that possible etiologies for R.P.'s TM remained "[e]ither primary viral or postinfectious on an autoimmune basis." *Id.* Additional lab tests were negative for syphilis, IgG, HSV-1 IgG, influenza viral A IgG and IgM antibodies, salmonella, shigella, e. coli, and campylobacter jejune. Ex. 5 at 41; Ex. 8 at 191, 204, 215, 248.

[3] *See* Ex. 8 at 24 (noting R.P. received the Fluzone version of the flu vaccine, lot #u4483ba).

A follow-up MRI conducted on January 24, 2013, showed less signal abnormality in R.P.'s posterior cord. Ex. 5 at 61. During his hospitalization, R.P. required a bronchoscopy for persistent right lobe atelectasis, as well as a multiple feeding tubes. Ex. 5 at 56; Ex. 8 at 107, 132. He was extubated on January 29, 2013, and his respiration improved thereafter. Ex. 5 at 67, 91. His ability to swallow gradually improved, and at the time of discharge on February 6, 2013, R.P. was drinking five to eight ounces of breast milk per day. *Id.* at 91. Given his improvement, treaters planned to remove the feeding tube within a week. *Id.*

R.P. was thereafter transferred to Gillette Children's Hospital ("Gillette") on February 6, 2013, for three days of inpatient physical therapy to improve strength in his trunk and extremities, as well as his range of motion, mobility, and ability to swallow. Ex. 4 at 1-11. He was ultimately discharged home on February 9, 2013 (one month following his admittance to the hospital). *Id.* at 5, 8-9. His final discharge diagnosis was "[t]ransverse [m]yelitis, [s]uspected [vi]ral [e]tiology." *Id.* at 9.

Treatment Following TM Diagnosis

Following his discharge from Gillette, R.P. went back to his pediatrician, Dr. Tio, on February 11, 2013, for monitoring of his symptoms. Ex. 8 at 243. Dr. Tio noted that R.P. had regained strength in his upper extremities but was not moving in his lower extremities. *Id.* The next day, R.P. returned to Gillette for a follow-up outpatient physical therapy session. Ex. 4 at 36. The Palattaos reported that R.P. had been steadily improving, with sporadic leg movements and had attempted to sit up for three to five seconds. *Id.* It was also noted that his feeding tube had been removed, and he was gaining weight. *Id.* R.P. continued to receive physical, occupational, and pool therapy through April 2013, and showed notably improvement in his upper extremities during that time. *Id.* at 43.

Treater Speculation as to Etiology for R.P.'s TM

On March 6, 2013, R.P. presented to a neurologist, Dr. Steven Janousek of Noran Neurological Clinic in Minneapolis, Minnesota, for treatment relating to his lingering symptoms. Ex. 9 at 4. Dr. Janousek noted that R.P. had regained some movement in his upper extremities, but that his prognosis remained unclear. *Id.* Upon exam, R.P. was noted to have normal deep tendon reflexes and appropriate head control, but very limited movement in his lower extremities. *Id.* Following the appointment, Dr. Janousek referred R.P. to Dr. Ralph Shapiro, of the Midwest Immunology Clinic, for an immunologic assessment. *Id.*

At the first visit to the Midwest Immunology Clinic on March 19, 2013, R.P. was evaluated by Kristin Epland, FNP-C (as Dr. Shapiro did not have an opening for several months). Ex. 6 at 1-4. The health history recorded during this visit is generally consistent with R.P.'s earlier-in-time

records. *Id.* In short, Mrs. Palattao recounted that R.P. had been prescribed antibiotics in December 2012 (due to family Christmas travels). *Id.* The URI symptoms he had been experiencing at the time subsequently resolved, and R.P. was well until around 3:00 AM on January 8, 2013 (the morning after his vaccinations), when R.P.'s mother found him "whimpering" with a fever around 100 degrees. *Id.* R.P.'s mother administered Tylenol and took him to daycare later that morning (as he seemed to have improved). *Id.* However, by 6:00 PM on the evening of January 8th, R.P. was reported to be "limp and unable to sit independently or hold his head up." *Id.* His temperature was again elevated to 100 degrees and his breathing appeared labored, so R.P.'s parents took him to the ER, where he was examined and discharged after a normal chest x-ray. *Id.* Thereafter, his condition deteriorated (including poor muscle tone/limpness and weak cry and cough), and R.P. presented a second time to the ER the following day, after which he was admitted to the intensive care unit and subsequently assessed with TM. *Id.* at 1-2.

Upon exam, Nurse Practitioner Epland noted that R.P. had recently completed a second round of antibiotics for purulent rhinitis since being discharged from the hospital five weeks prior. Ex. 6 at 2. Based on his health history, she assessed R.P. with TM "*temporally* related to his vaccinations." *Id.* at 4 (emphasis added). Nurse Practitioner Epland encouraged the Palattaos to "make contact with the vaccine injury fund as he would likely be a candidate for compensation." *Id.* She otherwise recommended that R.P. start a third round of antibiotics and planned to schedule an immunity lab panel in three months (given R.P.'s receipt of immune-modifying treatment during his hospitalization). *Id.*

R.P. and his parents returned to Midwest Immunology for an appointment with Dr. Shapiro three months later, on June 23, 2013. Ex. 6 at 5. During the visit, R.P.'s parents reported a health history consistent with the records discussed above. However, they relayed a slightly different history with regard to his December 2012 URI. Specifically, R.P.'s parents now stated that the December URI was "minimal and [R.P.] had a complete recovery within a very brief period of time." *Id.* at 6; *but see* Ex. 8 at 31 (parents reported in December 2012 that R.P.'s cold/cough symptoms had been ongoing for three weeks). It was noted that Amoxicillin was prescribed for the symptoms "because of fluid present behind [R.P.'s] tympanic membranes and he was to travel for Christmas." Ex. 6 at 5.

Dr. Shapiro opined that R.P. had "suffered an immune-based attack of his spinal cord (transverse myelitis) immediately after receiving his third set of routine immunizations," and that it was "reasonably certain" the immunizations triggered the response. Ex. 6 at 8. Dr. Shapiro noted that this opinion was the result of his review of R.P.'s history, testing results, and his own examination of R.P., although he added that "there were no other significant related events." *Id.* To explain how the vaccine-triggered response had occurred, Dr. Shapiro proposed that R.P. "was sensitized with his initial [two] immunizations and had a secondary immune reaction to the third which explain[ed] the immediate nature of his symptoms," although he added that the "reason for

the breach [of] his blood brain barrier [was] uncertain." *Id.* Dr. Shapiro recommended withholding all future immunizations and discussed possible triggers that cause a reoccurrence of symptoms (including infection, stress, contact dermatitis, or immunization). *Id.* Additional lab work, including an immunodeficiency panel, revealed normal results. *Id.* at 9-10.[4]

On April 9, 2013, R.P. presented to Dr. Tio for his nine-month well-baby visit. Ex. 8 at 256. Upon exam, R.P. was still unable to move his legs, but otherwise appeared healthy and was developing normally. *Id.* at 256-58. There was also some discussion concerning the Vaccine Program during this visit and the possibility of bringing a Program claim. It was recommended that R.P. return in four months for his twelve-month-old well visit. *Id.* at 258. Follow-up MRIs of R.P.'s spine were conducted on June 23, 2013, and revealed normal imaging compared to the prior studies recorded during his hospitalization in January. Ex. 9 at 21-22.

On July 20, 2013, R.P. (now twelve months old) presented for a follow-up appointment with his treating neurologist, Dr. Janousek, at which time Mrs. Palattao requested that he author a letter concerning his opinions regarding the cause of R.P.'s TM. Ex. 9 at 23. According to Dr. Janousek, R.P.'s health history revealed that he received vaccinations "shortly before the onset of his symptoms" and was subsequently diagnosed with TM thereafter. *Id.* Dr. Janousek's letter concluded that "it was more likely than not that [R.P.]'s myelitis and resultant disability was a consequence of his immunizations." *Id.* He relied, however, primarily on the fact that "no other cause had been determined," and that immunization-related TM had been documented in the literature. *Id.*[5]

II. Witness and Expert Testimony

A. *Angela Palattao*

Angela Palattao provided witness affidavits in support of Petitioners' claim. *See* Affidavit of Angela Palattao, dated August 14, 2013, filed as Ex. 13 (ECF No. 4) ("First Aff."); Affidavit of Angel Palattao, dated Sept. 7, 2013, filed as Ex. 57 (ECF No. 48-2) ("Second Aff."). She also testified in person at the entitlement hearing, and was the only direct fact witness to testify. Tr. at 5-57.

Mrs. Palattao confirmed most of what is reflected in the medical records, specifically testifying to the fact that R.P. was a healthy baby prior to his vaccinations and that he had experienced a normal birth, and was healthy and developmentally normal prior to his January 2013

[4] Upon examination, Dr. Shapiro also noted that R.P.'s testing showed a lack of IgM antibody to Hep A, which he determined to be unrelated to his subsequent TM. Ex. 6 at 5.

[5] Dr. Janousek's letter is also filed as Exhibit 11.

vaccinations. Tr. at 7-13. On January 7, 2013, Mrs. Palattao recalled presenting to Dr. Tio for R.P.'s six-month well-baby visit. *Id.* at 22. She reported that R.P. was healthy at the time of the visit and completed multiple developmental milestones, including unassisted sitting, rolling over, and passing objects from hand-to-hand. *Id.* at 23. Following R.P.'s receipt of his six-month vaccinations, Mrs. Palattao reported that he appeared normal for the remainder of the day, but experienced some increased fussiness. *Id.* at 24, 38. Mrs. Palattao reported that she administered Tylenol for the fussiness, but noted that R.P. was still feeding and voiding normally throughout the evening. *Id.* at 24-25.

On the morning of January 8th, Mrs. Palattao testified, R.P. was still experiencing increased fussiness,[6] but was acting normally otherwise when dropped off at daycare. Tr. at 25, 38-39. According to Mrs. Palattao, she picked R.P. from daycare around 5:00 PM that evening and found him to be more lethargic (which she reported was not typical, as R.P. was normally very happy and active). *Id.* at 26. She also indicated some concern regarding his apparent inability to sit up or play, but denied that R.P. appeared limp or weak. *Id.* at 27, 40-42. Respondent specifically questioned Mrs. Palattao about a telephone call (Ex. 8 at 39) made to R.P.'s treating pediatrician on January 8th (just prior to his initial ER presentation that evening). Tr. at 41-42. Notes from the call indicate that the Mrs. Palattao reported R.P. had been limp and was unable to move (Ex. 8 at 39), but Mrs. Palattao asserted that she observed him only to be lethargic. Tr. at 41-42. Mrs. Palattao was also asked about a daycare note referenced in the ER record (Ex. 5 at 1) stating that R.P. had experienced decreased urine output throughout January 8th, but argued this only meant that he had not taken as many bottles that day. *Id.* at 43-44. She otherwise asserted that she was indeed diapering R.P. that day. *Id.* at 54.

The Palattaos reported to the emergency room around 6:00 PM that evening out of concern for the aforementioned symptoms (in addition to breathing troubles). Tr. at 27-28, 41. Mrs. Palattao reported that the treating ER physician assessed R.P. with a localized vaccine reaction, and discharged R.P. around 8:30 PM that evening following a normal exam. *Id.* at 29-30, 55-56. R.P. otherwise behaved normally during the evening of January 8th. *Id.* at 30. He was still feeding and she noticed no urinary retention or change in his bowels at that time. *Id.*

By the morning of January 9th, however, R.P. was still experiencing the same concerning symptoms that prompted the ER visit the previous night (including lack of energy and trouble breathing). Tr. at 32-33. On cross, Mrs. Palattao also reported an onset of limpness, weakness, and decreased urine output by 10:00 AM on the morning of the 9th. *Id.* at 47-48. Mrs. Palattao further testified that she and her husband returned to the ER with R.P. around noon on the 9th, and his course deteriorated from there. *Id.* at 33. R.P. was admitted to the PICU and intubated later that evening. *Id.* Following relevant testing, the diagnosis of TM was confirmed and R.P. was

[6] Mrs. Palattao's affidavit filed in support also noted that R.P. would cry when touched (during the evening of January 8th). *See* Tr. at 44-45; First Aff. at 2. At hearing, she clarified that this was intended to describe his fussiness. Tr. at 45.

hospitalized for roughly one month and completed a short stay at an inpatient rehab unit. *Id.* at 34, 49.

Mrs. Palattao also described R.P.'s current condition as of May 2018. R.P. (now five years old) is paralyzed from the mid-chest down and requires daily use of a wheelchair. Tr. at 6. He is fully dependent on his parents for his primary care. *Id.* Accordingly to Mrs. Palattao, R.P. recently had surgery to help with control over his bladder and bowels. *Id.* She otherwise described him as "willful, energetic, and spunky." *Id.* He attends preschool five days a week and enjoys spending time with his classmates. *Id.*

Apart from the above, Mrs. Palattao also clarified her recollection of events and the medical records with regard to R.P.'s pre-vaccination URI (or mild cold symptoms). According to Mrs. Palattao, R.P.'s father took him in for an examination on December 21, 2012, in part because R.P. was "pulling on his right ear." Tr. at 16, 36-37. The medical record does not reflect a complaint of ear tugging, however, discussing only cough and cold symptoms. *See* Tr. at 37 (citing Ex. 8 at 31). The family was expecting to travel for the Christmas holiday and Mrs. Palattao felt it would be best to have R.P. evaluated prior to the trip. *Id.* at 17-18, 36. Mrs. Palattao suggested that R.P.'s pediatrician found some fluid behind the ear, but nothing too notable. *Id.* at 17. She explained that R.P.'s treater prescribed Amoxicillin as a precaution given R.P.'s discomfort and the family's travel plans. *Id.* at 17-18. Otherwise, no immediate concerns were noted by R.P.'s pediatrician or his parents. *Id.* at 18-19. She subsequently administered the antibiotic as directed, adding that R.P.'s ear tugging resolved within a couple of days. *Id.* at 19.

B. *Dr. Marcel Kinsbourne*

The first of Petitioners' two experts, Dr. Marcel Kinsbourne, M.D., filed three written reports and testified via videoconference at hearing. *See* Expert Report, dated Dec. 27, 2013, filed as Ex. 14 (ECF No. 12-1) ("First Kinsbourne Rep."); Expert Report, dated Mar. 24, 2014, filed as Ex. 17 (ECF No. 22-2) ("Second Kinsbourne Rep.")[7]; Expert Report, dated Apr. 5, 2018, filed as Ex. 76 (ECF No. 76-1) ("Third Kinsbourne Rep."). Dr. Kinsbourne opined that the R.P.'s January 2013 vaccinations (most likely the DTaP vaccination in his estimation)[8] caused his TM.

As his CV indicates, Dr. Kinsbourne is a pediatric neurologist. CV, filed as Ex. 15 (ECF No. 12-2) ("Kinsbourne CV"). He received his medical degree in England, and he has been

[7] Dr. Kinsbourne's first report (dated December 2013) and his second report (dated March 2014) are identical. The March 2014 report was filed to remove language related to a Hep B vaccination (as R.P. did not receive this vaccine). Dr. Kinsbourne acknowledged this correction in his testimony at hearing. *See* Tr. at 89-90; Second Kinsbourne Rep. at 1, 3, 6.

[8] Dr. Kinsbourne's testimony was primarily limited to the DTaP vaccine (and specifically its tetanus components). At times, however, he also suggested the flu vaccine (or the multiple vaccines in combination that R.P. received on January 7, 2013) might also have played a role. Tr. at 70, 349. In his view, because all vaccines cause innate immune responses, it can be difficult to differentiate between their effects when given as a group. *Id.* at 349.

licensed to practice medicine in North Carolina since 1967. *Id*. at 2; Tr. at 60. From 1967 to 1974, Dr. Kinsbourne served as an associate professor in pediatrics and neurology and a senior research associate at Duke University Medical Center before holding a series of academic positions, including professorships in pediatrics, neurology, and psychology. Kinsbourne CV at 2. His clinical experience includes serving as a senior staff physician in Ontario from 1974-1980, and a clinical associate in neurology at Massachusetts General Hospital from 1981-1991. *Id.* at 2-3. Dr. Kinsbourne has experience treating pediatric patients with TM, although (as noted in other Vaccine Program cases) twenty years (or more) have passed since he regularly saw patients. Tr. at 85-86. He has published several articles examining neurological diseases (though none directly addressing TM), and he is on the editorial board of several journals, such as *Brain and Cognition* and *Archives of Clinical Neuropsychology*. Kinsbourne CV at 4, 7-40.

At hearing, Dr. Kinsbourne began his testimony by describing TM and its common clinical symptoms. Dr. Kinsbourne characterized TM as an inflammatory, demyelinating disorder of the spinal cord. Tr. at 68; Second Kinsbourne Rep. at 3. In TM, the spinal cord's nerve fibers lose their myelin sheath, thereby resulting in a loss of cell communication between the muscles and the body's nerve endings up to the brain. Tr. at 68. According to Dr. Kinsbourne, TM has many potential triggers (including a bacterial infection, viral illness, genetic abnormalities, and in certain circumstances, a vaccine). *Id.* at 70; Second Kinsbourne Rep. at 3-4.[9]

A typical course of TM can include motor weakness, sensory abnormalities (referable to the spinal cord), bladder dysfunction, and paresthesia. E. Frohman, et al., *Transvers Myelitis*, 63 New Eng. J. Med. 564, 565 (2010), filed as Ex. 21 (ECF No. 65-2). TM is often monophasic, meaning it begins abruptly and impacts the white matter of the brain (as opposed to the gray matter). Tr. at 69. Recovery is highly variable from patient to patient, resulting in complete recovery in some cases, but permanent disability in others. *Id.*

Upon review of R.P.'s record, Dr. Kinsbourne opined that R.P.'s presenting symptoms were best categorized as acute TM of the "utmost severity." Tr. at 69. As the medical records filed in the case revealed, R.P. was developing normally prior to vaccination, and exhibited no adverse reaction to his first two rounds of childhood vaccinations. *Id.* After the third round, however, Dr. Kinsbourne opined, R.P. had a "striking, almost explosive onset" of TM. *Id.* Dr. Kinsbourne relied heavily on MRI evidence conducted during R.P.'s hospital stay (which confirmed the TM diagnosis), as well as his presenting symptoms over the course of his hospitalization (including lack of sensation and numbness of the limbs, trouble breathing, and the inability to void). *Id.* at 67, 91.

[9] At hearing, Dr. Kinsbourne offered some theory that a certain genetic defect, such as a polymorphism gene, could play some role in the initiation of TM (via immune dysfunction). Tr. at 72. On cross however, Dr. Kinsbourne acknowledged that R.P. was never tested for the above-mentioned genetic defect. *Id.* at 108-09. And the defect otherwise played no role in his theory in the present matter.

Dr. Kinsbourne theorized that R.P.'s TM was likely initiated by the tetanus toxoid component of the DTaP vaccine. Second Kinsbourne Rep. at 4-5, 7. It was then mediated by a "pathologic" effect of the innate immune system and induced by an overwhelming attack of proinflammatory cytokines on R.P.'s spinal cord.[10] Tr. at 71, 73, 105, 107-08, 343-44; Third Kinsbourne Rep. at 3. Dr. Kinsbourne categorized the innate immune response as the body's first defense to an immune challenge. Tr. at 71, 74, 77, 345; Third Kinsbourne Rep. at 2.[11] Components of the innate immune system include macrophages,[12] cytokines,[13] and neutrophils,[14] for example. Tr. at 71, 345, 359. Dr. Kinsbourne explained that when the body encounters a foreign protein (i.e. a bacterium or virus), the immediate innate response signals macrophage-mediated TLRs (or "toll-like receptors") producing proinflammatory cytokines (distinct from the T cell/B cell components of the adaptive immune system). *Id.* at 71, 76-77. According to Dr. Kinsbourne, proinflammatory cytokines typically cause localized inflammation at the injection site (along with generalized lethargy and fever if released into the bloodstream, similar to those symptoms R.P. experienced). *Id.* at 71, 350, 356.

In most cases, the production of proinflammatory cytokines after vaccination is perfectly harmless and actually aids the immune system in establishing immunity against a particular disorder that the vaccine is intended to secure. Tr. at 71, 345. In rare cases, however, Dr. Kinsbourne opined, the effect of proinflammatory cytokines can be excessive and dangerous (or "toxic"), resulting in a secondary autoimmune (or inflammatory) disease process (i.e. TM). *Id.* at 71, 108. According to Dr. Kinsbourne, the brain (functioning normally), has multiple methods of regulating cytokines so that they exert a beneficial effect, rather than endanger the host. *Id.* However, unrestrained cytokines can migrate from the peripheral nervous system, breach the blood brain barrier ("BBB"), and then attack components of the central nervous system (i.e. the brain,

[10] Dr. Kinsbourne testified that he is not invoking the mechanistic process of molecular mimicry in the present case. Tr. at 105. His report, however, makes reference to the concept as a possible biologic explanation for onset of TM post-vaccination. Second Kinsbourne Rep. at 5. He also cited to various pieces of literature addressing molecular mimicry. *See, e.g.*, K. Stratton, et al., *Adverse Effects of Vaccines: Evidence and Causality*, Institute of Med. (2002), filed as Ex. 31 (ECF No. 25).

[11] The adaptive immune system, by contrast, initiates a protective response at a much slower rate (i.e. days to months) by recognizing specific antigens. Tr. at 250-51. The adaptive system is made of both B cells (which make antibodies against the foreign protein) and T cells (that help eliminate diseased cells). *Dorland's Illustrated Medical Dictionary* 315, 324, 1084 (32nd ed. 2012) (hereinafter, "*Dorland's*").

[12] Macrophages are mononueclear phagocytes that kill and digest foreign invaders during an immune response. *Dorland's* at 1093.

[13] Cytokines are nonantibody specific proteins released by cells upon contact with a foreign antigen. *Dorland's* at 466. They act as intercellular mediators in an immune response. *Id.*

[14] Neutrophils are white blood cells that patrol the bloodstream and attack foreign antigens (including viral and bacterial). *See Neutropenia*, Mayo Clinic, https://www mayoclinic.org/symptoms/neutropenia/basics/definition/sym-20050854 (last accessed on Jan. 10, 2019).

spinal cord, or both), resulting in some form of demyelinating disease in rare cases. *Id.* at 72, 108, 355, 357.[15] Once across the BBB, these cytokines induce microglia[16] and other astrocytes[17] to produce more cytokines thereby causing the demyelination of axons and death of oligodendrocytes. *Id.* at 351; Third Kinsbourne Rep. at 3.

Dr. Kinsbourne asserted that the chief proinflammatory cytokines applicable to the present case are IL-6, IL-1 beta, TNF alpha, and IL-17. Tr. at 73; Second Kinsbourne Rep. at 4. He described IL-1 beta and TNF alpha as "stimulat[ors]" or generators of IL-6, whereas IL-17 "regulates" all three. Tr. at 73, 75, 350-51; Third Kinsbourne Rep. at 3. The IL-6 cytokine, however, was determined to be "necessary and sufficient to cause [TM]" (or the "active destructive influence"). Tr. at 73, 75, 351. Following vaccination, Dr. Kinsbourne opined that astrocytes produce IL-6 in response to direct stimulation by TNF alpha and IL-1 beta, causing a significant release of cytokines into the blood stream (resulting in a breach of the BBB and eventual attack on the spinal cord). Second Kinsbourne Rep. at 5; Tr. at 351. Dr. Kinsbourne acknowledged that the trigger for the initial production of IL-6 in astrocytes is still being investigated. *Id.* at 6. He maintained, however, that currently literature supports his contention that a vaccination could be a potential instigator. *Id.*

In support of his contention that vaccines can cause the production of proinflammatory cytokines, Dr. Kinsbourne referenced the Kashiwagi paper. *See* Y. Kashiwagi, et al., *Production of Inflammatory Cytokines in Response to Diphtheria-pertussis-tetanus (DPT), Haemophilus Influenza Type B (Hib), and 7-Valent Pneumococcal (PCV7) Vaccines*, 10 Human Vaccines & Immunotherapies 677 (2014), filed as Ex. 46 (ECF No. 72-6) ("Kashiwagi"). Kashiwagi was an *in vitro* study comparing the levels of inflammatory cytokines in the sera of 61 vaccine recipients with febrile illness, against 18 recipients without febrile illness, 24 hours post vaccine administration. Kashiwagi at 677. The study's authors tested the peripheral blood cultures of the 61 patients by (separately and concurrently) introducing combinations of the DPT, Hib, and/or PCV7 vaccines in order to determine the levels of cytokine production in the cell cultures. *Id.* Researchers found that concurrent stimulation with combinations including Hib/PCV7 and

[15] Dr. Kinsbourne's explanation for *how* cytokines cross from the periphery through the BBB and into the central nervous system was both vague and conclusory. At hearing, Dr. Kinsbourne asserted that cytokines cross the BBB via an unspecified "mechanism" and once there stimulate CNS microglia to "eject proinflammatory cytokines in the CNS space" (including IL-6). Tr. at 355. He did not further explain the "mechanism" responsible for their transportation, and he cited no scientific literature or evidence suggesting that proinflammatory cytokines originating in the periphery can actually be stimulated in levels high enough to function in this matter. *See id.* at 358 ("everyone in the field knows" that "certain substances" can cross the BBB and are assisted by "processes which are specific to them"). Dr. Kinsbourne similarly did not fully indicate how long it would take cytokines in the periphery to cross the BBB (from the time of stimulation to resulting viewable symptomology). He made some suggestion that process could occur rather quickly and not drag on "day after day," but could not be more specific. *Id.* at 357.

[16] Microglia are CNS cells that act as macrophages and scavenge various intruders (including infectious agents and waste products of nerve tissue). *Dorland's* at 1159.

[17] Astrocytes or astroglia are CNS cells in the brain that support neuronal function by producing antioxidants, recycling neurotransmitters, and maintaining the BBB. *Dorland's* at 169, 170.

DPT/Hib/PCV7 produced higher levels of the TNF-alpha and human G-CSF cytokines. *Id.* Notably, however, Kashiwagi's authors noted that *only* Hib induced increased levels of IL-6 post-vaccination, with no significant differences in production of IL-6 was noted in response to stimulation by the DPT or PCV7 vaccines. *Id.* at 679. Overall, testing in Kashiwagi indicated there was "no significant difference . . . observed in IL-6 production with the single or concurrent stimulation" of DPT, Hib, and or PCV7. *Id.*

To link the IL-6 cytokine to the pathologic process resulting in TM, Dr. Kinsbourne relied on a different study. *See* A. Kaplin, et al., *IL-6 Induces Regionally Selective Spinal Cord Injury In Patients With the Neuroinflammatory Disorder Transverse Myelitis*, 115 J. Clin. Invest. 2731 (2005), filed as Ex. 22 (ECF No. 65-3) ("Kaplin I"); Third Kinsbourne Rep. at 3. Kaplin I researchers conducted a cytokine antibody array for six patients presenting with acute, idiopathic TM (prior to any immunotherapy treatment), contrasting their findings with eight healthy patients. Kaplin I at 2733. Researchers found that the cytokine IL-6 was elevated 300-fold within the CSF of TM patients (whereas all other cytokine levels were altered less than 10-fold). *Id.* at 2733, 2738. Two TM patients in the study died from respiratory failure. *Id.* Following their autopsies, researchers performed postmortem immunohistochemical staining of the spinal cord of both patients to determine the source of the IL-6 production. *Id.* at 2733. In both cases, researchers found that the increased IL-6 was induced by astrocytes "in and around the area of inflammation within the spinal cord" (i.e. within the CNS). *Id.* Serum absorption levels also supported this finding. *Id.*

Kaplin I researchers also conducted an animal model study to determine if IL-6 was sufficient to cause cellular injury in the spinal cord (and thus produce symptoms attributable to TM). To test this, researchers added CSF from a TM patient to culture spinal cord sections of rats. Kaplin I at 2733-34. Researchers next injected high levels of IL-6 (24ng of IL-6 for seven days) directly into the rat spinal cords and compared those results to rat spinal cords infused directly with a saline solution. *Id.* at 2735. Based upon an eight-day observation period, researchers found that the rats injected directly with IL-6 displayed an onset of demyelination and neuronal damage (including a 50% loss of both hind leg strength) characterized by swollen, empty myelin-encased chambers after two days. *Id.* Relying on the above, Kaplin I's authors concluded that the IL-6 cytokine "is a critical determinant of patient outcome in TM[,]" though they could not affirmatively state the *source* of the IL-6 stimulation, acknowledging that it remained a subject of investigation. Kaplin I at 2738-39. They did, however, offer various biological hypotheses for such an increase – including an antecedent infection, genetic differences, or an immune response following vaccination. *Id.*

For the assertion that IL-6 could be stimulated as a result of an immune response post-vaccination, Dr. Kinsbourne referenced a second paper also co-authored by Kaplin. *See* A. Kaplin, et al., *Diagnosis and Management of Acute Myelopathies*, 11 Neurologist 2 (2005), filed as Ex. 49 (ECF No. 73-1) ("Kaplin II"). Kaplin II cites to two case reports of TM following receipt of a flu vaccine and a booster Hep B vaccine. Kaplin II at 4. The Kaplin II article also referenced autopsy

reports of post-vaccination TM which revealed elevated levels of lymphocytic infiltration of the spinal cord. *Id.* Despite the above, Kaplin II cautioned against any over reliance on the cited case reports within the article (as extensive data sets show vaccines are not associated with an increased incidence of neurologic complication). *Id.* Kaplin II otherwise acknowledges that increased IL-6 has been associated with TM, but does not offer further comments regarding the source of its stimulation. *Id.* at 5.

Besides the above, Dr. Kinsbourne also referenced a third item of literature purporting to associate IL-6 to TM. *See* Graber, et al., *Interleukin-17 in Transverse Myelitis and Multiple Sclerosis*, 196 J. Neuro. Immunol. 124 (2008), filed as Ex. 69 (ECF No. 63-3); Third Kinsbourne Rep. at 3. Similar to Kaplin I and II, Graber's authors noted that IL-6 cytokine levels have been shown to be increased in the CSF of TM patients. Graber at 124. Researchers in Graber sought to determine if the IL-17 cytokine was similarly elevated in TM patients (given it is role as a regulator of the IL-6, TNF-alpha, and IL-1 beta cytokines) in an attempt to link IL-17 cytokines to a CNS IL-6 cascade. *Id.* at 124, 131. To test the above, researchers measured the IL-17 and IL-6 levels in the peripheral blood of 13 TM patients along with 37 multiple sclerosis ("MS") patients. *Id.* at 125. Upon review of the peripheral blood cytokine assays, the Graber authors found both an increase in IL-17 and IL-6 in the CSF of both MS and TM patients. *Id.* From this, it was determined that IL-17 could potentially stimulate initial IL-6 production, but that *only* IL-6 could "induce IL-6 production by astrocytes." *Id.* 125, 131. Graber too, however, could not identify what specifically triggers the increased production. *Id.* at 130 ("immunodepletion of IL-6 . . . did not completely suppress astrocyte IL-6 production, suggesting other soluble factors may also be involved"). Graber also does not implicate any vaccine as playing a role in the simulation of IL-17 or IL-6.

Dr. Kinsbourne next referenced various review articles investigating the role a vaccine could play in initiating an overproduction of cytokines sufficient to result in TM. *See, e.g.*, N. Agmon-Levin, et al., *Transverse Myelitis and Vaccines: A Multi-Analysis*, 18 Lupus 1198, 1199 (2009), filed as Ex. 52 (ECF No. 73-4) ("Agmon-Levin"); Second Kinsbourne Rep. at 4. Agmon-Levin catalogued 37 case reports of TM following vaccination (four of which followed the DPT or DT vaccine). Another article discussed various case studies reporting an onset of acute TM following vaccine administration (but involved *only* the flu or booster Hep B vaccines). *See* D. Kerr, et al., *Immunopathogenesis of Acute Transverse Myelitis*, 15 Current Op. In Neuro. 339, 340-41 (2002), filed as Ex. 24 (ECF No. 65-4) ("Kerr"). A third review article found that 38 percent of a 47-patient population *reported* immunization within 30 days prior to onset of TM. *See* F. Pidcock, et al., *Acute Transverse Myelitis in Childhood: Center-Based Analysis of 47 Cases*, 68 Neurology 1474, 1479 (2007), filed as Ex. 26 (ECF No. 65-5) ("Pidcock"); Second Kinsbourne Rep. at 4. Pidcock, however, generally found no "significant relationship" between vaccination and TM (given the high incidence of immunization in the pediatric population generally). Pidcock at 1479. Agmon-Levin and Kerr similarly noted that extensive data sets suggested that vaccinations are *not* associated with an increased incidence of neurological disease, and thus

cautioned against over reliance on the conclusion (hinted at by the various case reports they reviewed) that TM is vaccine-induced. Agmon-Levin at 1202; Kerr at 341.

Notably, Dr. Kinsbourne also filed literature directly *contradicting* the case reports discussed in Agmon-Levin, Kerr, and Pidcock. The Baxter article (an epidemiological study), for example, reviewed nearly 64 million vaccine doses cataloged by the Vaccine Safety Datalink and found no safety concern or association between vaccination and onset of TM. *See* R. Baxter, et al., *Acute Demyelinating Events Following Vaccines: A Case-Centered Analysis*, 63 CID 1456, 1461 (2016), filed as Ex. 65 (ECF No. 58-4).

Besides the case reports mentioned in Agmon-Levin, Dr. Kinsbourne's second report cited some specific case reports of onset of TM following administration of a tetanus-containing vaccine. Second Kinsbourne Rep. at 4-5; *see, e.g.*, E. Whittle, et al., *Transverse Myelitis After Diphtheria, Tetanus, and Polio Immunization*, 4 Brit. Med. J. 1450 (1977), filed as Ex. 36 (ECF No. 68-1) ("Whittle") (seven month-old developed TM six to seven days following Td/polio vaccine); R. Riel-Romero, *Acute Transverse Myelitis in a 7-month-old Boy After Diphtheria-Tetanus-Pertussis Immunization*, 44 Spinal Cord 688 (2006), filed as Ex. 28 (ECF No. 65-7) ("Riel-Romero") (seven month-old developed TM following DPT vaccine; admitted to hospital 17 days after vaccination)[18]; S. Savas, et al., *Transverse Myelitis Following Diphtheria Tetanus Toxoids (Td) Vaccination: A Case Report*, 59 Turk. J. Physical Med. & Rehab. 349 (2013), filed as Ex. 74 (ECF No. 68-6) ("Savas") (46 year-old developed TM following Td vaccine, with onset in two hours and symptoms lasting six months before individual sought medical intervention); S. Read, et al., *Acute Transverse Myelitis After Tetanus Toxoid Vaccination*, 339 Lancet 1111 (1992), filed as Ex. 27 (ECF No. 65-6) (50 year-old developed TM following tetanus toxoid vaccination).[19] Despite the above, Dr. Kinsbourne agreed that case reports cannot prove causality on a scientific level, while insisting that they nevertheless bulwarked Petitioners' contention that a vaccine was a likely cause where no other reasonable trigger was established. Tr. at 99, 360.

As to the timing of onset of TM post-vaccination, Dr. Kinsbourne maintained that the production of proinflammatory cytokines would happen "almost immediately" following vaccine

[18] Riel-Romero significantly allowed for the likelihood that the subject of the study had developed TM due to a URI he had experienced within two weeks of vaccination. Riel-Romero at 690. The article also admits that causality between vaccine and TM could not be assumed simply on the basis of the temporal association. *Id.*

[19] More broadly, Dr. Kinsbourne referenced some case reports of other neurologic injuries (presumably based on the contention that they are comparable) sustained following tetanus-containing vaccines. *See, e.g.*, H. Topalogu, et al., *Optic Neuritis and Myelitis After Booster Tetanus Toxoid Vaccination*, 339 Lancet 178 (1992), filed as Ex. 55 (ECF No. 73-7) (case report of 11 year-old who developed optic neuritis/myelitis following booster tetanus toxoid vaccine with onset of twenty hours); D. D'Costa, *Transverse Myelitis Following Cholera, Typhoid and Polio Vaccination*, 83 J. Royal Soc. Med. 653 (1990), filed as Ex. 73 (ECF No. 68-5) (case report of 24 year-old who developed TM following OPV/cholera/typhoid vaccine with onset of 24 hours); N. Abdul-Ghaffar, et al., *Brown Séquard Syndrome Following Diphtheria and Tetanus Vaccines*, 24 Trop. Doct 74, 74-75 (1994), filed as Ex. 71 (ECF No. 68-3) (case report of 13 year-old who developed a rare neurologic condition involving spinal cord lesions following Td vaccination with onset of 36 hours).

administration. Tr. at 75, 117. In his estimation, reasonable scientific literature suggested that an innate immune response could occur between six hours post-vaccination to a maximum of two days later. *Id.* at 77, 109.[20] For support, Dr. Kinsbourne cited to various case reports showing an onset of TM after receipt of a tetanus-containing vaccine within hours to days/weeks following administration. *See, e.g.*, Agmon-Levin at 1200 (three case reports of months-old children who developed TM between six and seventeen days post-vaccination); Savas at 349 (46 year-old developed TM two hours following Td vaccine). Dr. Kinsbourne acknowledged that he had not filed any evidence in support of a six-hour onset, but maintained that there existed various studies that would support such a rapid onset. *Id.* at 109-111. He did, however, admit that two hours would be too soon to be medically plausible. *Id.* at 110.

Dr. Kinsbourne's three expert reports offered varying statements regarding the most likely onset for R.P.'s initial TM symptoms. *See, e.g.*, First Kinsbourne Rep. at 6 (R.P.'s TM began "less than two days" following receipt of his vaccinations); Second Kinsbourne Rep. at 4 (R.P.'s TM "began less than 36 hours after a DTaP vaccination"). At hearing, however, Dr. Kinsbourne highlighted evidence in R.P.'s medical records that he maintained supported the conclusion that onset of his neurological disease process began sometime within 48 hours of vaccination – most likely sometime between his initial January 8th ER visit and the return ER visit on January 9th (or 36 to 48 hours following vaccine administration). *Id.* at 347-48.

In so maintaining, Dr. Kinsbourne acknowledged that Mrs. Palattao had reported concerning symptoms to Dr. Tio's office on January 8th (including an inability to sit up, labored breathing, pain when touched, lethargy, decreased urine output, and weak crying) – *less* than 36 hours post-vaccination. Tr. at 92-93. However, he noted that R.P.'s initial neurological exam on the 8th was normal (revealing normal tone and power). *Id.* at 92, 94, 347. He therefore argued that R.P.'s symptoms at his initial presentation on January 8th (and even those he experienced the evening of the 7th) were distinguishable from those he experienced on January 9th (which now included arm weakness, numbness, and decreased tone), and that such symptoms plus the confirming MRI imaging made onset most likely to have occurred later. *Id.* at 91-92, 94, 117. He also suggested the MRI imaging indicated demyelination "very high up in the cervical area and the thoracic area" which would be more consistent with arm weakness – not the purported decreased urinary output as suggested in records from January 8th, which he deemed associated with the lower portion of the spinal cord. *Id.* at 93-94. Overall, Dr. Kinsbourne maintained that R.P.'s earlier symptoms (while *still* vaccine related) were not wholly neurologic in nature. *Id.* at 93, 347; Third Kinsbourne Rep. at 1-2. In so opining, however, Dr. Kinsbourne acknowledged a clear continuity between R.P.'s initial symptoms (i.e. fever and malaise) and those he experienced two days beyond. Tr. at 116-18, 351, 352.

[20] An adaptive immune response, by contrast, would require a minimum of four days to occur. Tr. at 77.

Consistent with the above, Dr. Kinsbourne disputed Respondent's expert's contention that R.P.'s January 8th symptoms (including crying/fever/touch sensitivity) could be evidence of "meningeal irritation" (or irritation of the membranes that wrap around the brain and spinal cord). Tr. at 79-80, 95. Based on his own review of the record, Dr. Kinsbourne found no treater support for such an assertion in the record. *Id.* Furthermore, he opined that any meningeal irritation R.P. experienced could be confirmed only by symptoms such as stiffness and rigidness or headache-associated pain (all of which R.P. did not experience). *Id.*

Although Dr. Kinsbourne did seem to lean in favor of an onset of neurologic symptoms on January 9th, at one point during Respondent's cross examination he opined that R.P.'s onset of TM *could* also have occurred within 36 hours post-vaccination. Tr. at 91. When asked to explain this, Dr. Kinsbourne referenced the concept of innate immune memory. Dr. Kinsbourne opined that innate immune system memory (or presensitization) might play a role in a quick time interval between vaccination and onset of symptoms. Tr. at 353-54; Third Kinsbourne Rep. at 3-4. According to Dr. Kinsbourne, R.P.'s innate immune system could have developed a memory from his receipt of the *third* DTaP vaccination, which upon stimulation could facilitate a significant (and more extreme) enough release of cytokines to cause TM within a two-day timeframe. Tr. at 74, 353-54; Third Kinsbourne Rep. at 4. Dr. Kinsbourne categorized this response as an anamnestic reaction, which he defined as an "accelerated and augmented production of specific antibody after reexposure to an agent . . . ." Third Kinsbourne Rep. at 4. (Of course, as noted above Dr. Kinsbourne in this case is not proposing that R.P.'s TM was mediated by an autoantibody response).

As an alternative explanation for a more rapid onset, Dr. Kinsbourne referenced a single item of literature. *See* M. Netea, et al., *Innate Immune Memory: A Paradigm Shift In Understanding Host Defense*, 16 Nature Immunol 675 (2015), filed as Ex. 68 (ECF No. 63-2) ("Netea"); Tr. at 353. Netea is a "meeting report" authored following the first Innate Immune Memory Conference in Hixton, Cambridge in March 2015. Netea at 675. Netea generally attempts to explore a self-described "new[]" concept (innate immune memory) which challenges the *accepted* scientific principle that the innate immune system mounts nonspecific immune responses to invading antigens (rather than an antigenic-specific response), without any conferred immunologic memory (a concept generally applicable to plants and invertebrates). *Id.*

According to Netea, the concept of innate immune memory (or "innate reprograming") proposes that the innate system has adaptive qualities capable of producing immune memory via a "priming response" where the innate system would be altered after first exposure to an antigen such that upon re-exposure to the same stimuli, it would display a heightened response in subsequent defense against that same invader. Netea at 675. Upon re-exposure to a priming event, chronic inflammation (initiated during an innate response) could "possibly" reprogram the microglia and astrocytes such that plaque clearance in the body is impaired (leading to an enhancement of NLRP3 inflammasome) and a resulting disease process. *Id.* Netea's authors suggest that vaccinations provide "some of the best evidence" of innate immune memory in

humans (given the resulting protective effects experienced upon receipt of a booster vaccine). *Id.* at 678-69. Overall, however, Netea does not implicate vaccines as capable of initiating a pathologic process via the innate system simply due to secondary exposure to it.

Finally, Dr. Kinsbourne spent some time at hearing discussing records pertaining to R.P.'s pre-vaccination health history, in an attempt to refute Respondent's contention that R.P.'s TM was triggered by a pre-vaccination viral illness (or his diagnosed ear infection). Tr. at 82-83, 350, 361. Rather, Dr. Kinsbourne categorized R.P.'s December 2012 respiratory symptoms as likely noninfectious fluid in the ear (given the lack of confirming viral evidence in the record) or an allergy. *Id.* at 83, 361-62; Third Kinsbourne Rep. at 1. R.P. had no fever or evidence of "systemic effect" of existing autoimmune process around that time (or any time prior to his hospital presentation). Tr. at 83, 361. Dr. Kinsbourne acknowledged that R.P.'s health record indicated that he was prescribed antibiotics for the symptoms experienced in December 2012, but he inferred from the record (and the mother's testimony) that this was a prophylactic attempt to avoid any bacterial infection occurring while the Palattaos travelled for the 2012 Christmas holiday. *Id.* at 84, 98; Third Kinsbourne Rep. at 1. Overall, given the lack of viral evidence in the record, Dr. Kinsbourne found it "very unconvincing" that R.P.'s symptoms in December 2012 could explain his TM. *Id.* at 361-62.

C. *Dr. Ralph Shapiro*

Petitioners' second expert was Dr. Ralph Shapiro. He filed two expert report and also testified at hearing. *See* Expert Report, dated May 28, 2015, filed as Ex. 38 (ECF No. 39-1) ("First Shapiro Rep."); Expert Report, dated Dec. 18, 2015, filed as Ex. 40 (ECF No. 41-1) ("Second Shapiro Rep.").[21] Like Dr. Kinsbourne, Dr. Shapiro opined that the record best supports the conclusion that R.P.'s TM was vaccine-induced, given the timing of injury and the lack of alternate explanation for R.P.'s symptoms. Tr. at 154-55, 310, 312.

Dr. Shapiro is the owner and medical director of the Midwest Immunology Clinic in Plymouth, Minnesota. Tr. at 120; CV, filed as Ex. 39 (ECF No. 39-2) ("Shapiro CV"). He completed his undergraduate and medical degrees at the University of Minnesota School of Medicine ("University"), followed by a three-year residency in pediatrics and a three-year fellowship in pediatric hematology and oncology. *Id.* at 120-21; Shapiro CV at 1. Following his fellowship, Dr. Shapiro was hired by the University as an instructor (and later assistant professor) in the pediatrics department. Shapiro CV at 1-2. During that time he helped develop the immunology section (and also treated immune deficient patients with cancer and storage disorders and performed bone marrow transplants). *Id.* at 121. He remained with the University from 1986 to 1996, and then entered a primary-care pediatric practice from 1995 to 1999. *Id.*; Shapiro CV at 2. Dr. Shapiro thereafter opened his own clinic in 2000 and limited his practice to pediatric and

[21] It appears that Exhibit 12 was also filed with the title of "expert report," but is simply a copy of Dr. Shapiro's treatment notes from R.P.'s initial examination (which were already filed under Exhibit 6). *See* Ex. 12 (ECF No. 4).

adult immunologic treatment. Tr. at 122. His clinic is designated as a Modell Center of Excellence for diagnosis and treatment of immune deficiency and he serves as the president of the Consortium of Independent Immunology Clinics. *Id.* at 124-45. Dr. Shapiro is licensed in the state of Minnesota and holds board certifications in pediatrics and pediatric hematology and oncology. *Id.* at 122-23; Shapiro CV at 2.

At hearing, Dr. Shapiro testified that he has conducted research on relevant topics (including immunosuppressive drugs and genetic immunodeficiencies), and has published extensively on the complications of immunosuppression following organ/bone marrow transplants (as well as pediatric oncology). Tr. at 123; Shapiro CV at 3, 5-17. He also has experience treating patients with neuroimmunologic conditions (as well as developing immunoglobulin treatment). Tr. at 163. Dr. Shapiro served as medical director of the Noran Clinic from 2003 to 2006 and assisted with developing an infusion center aimed at co-managing patients with both neurologic and immunologic conditions. *Id.* Over the course of his career, he estimated that he had treated around twenty patients with TM. *Id.* at 162. Dr. Shapiro testified that some of those patients were pediatric, but he could not remember an exact number. *Id.*

Dr. Shapiro began his testimony by recounting R.P.'s health history both prior to and following the January 7, 2013 vaccinations. Consistent with Dr. Kinsbourne's testimony, Dr. Shapiro testified that R.P. was relatively healthy prior to his vaccinations, but exhibited an overall decline in health thereafter. Tr. at 130. Dr. Shapiro first examined R.P. in June 2013 (almost six months following his receipt of his January 2013 vaccinations and ensuing onset of TM). Tr. at 126. R.P.'s treating pediatrician referred him to Dr. Shapiro with the goal of identifying a possible etiology for the TM. *Id.*

Upon initial exam, R.P. had poor motor function in his lower extremities, as well as weak reflexes, but was otherwise healthy. Tr. at 127-28. Dr. Shapiro ordered various lab testing (including white blood cell, IgA/IgM antibody, ANA, Hep A, and T cell counts) to determine if R.P. had any underlying immune problem, but testified that the results were unremarkable. *Id.* at 128-29, 131-32.[22] Dr. Shapiro found no evidence of a potential infectious cause in light of R.P.'s negative infectious disease panel conducted during his hospitalization. *Id.* at 132, 153-54. Based on his review of R.P.'s medical history and June 2013 evaluation, Dr. Shapiro opined, consistent with Dr. Kinsbourne, that R.P. likely experienced an autoinflammatory "immune-based attack of his spinal cord . . . after receiving [a] third set of routine immunizations." *Id.* at 128, 148. He could

[22] Notably, the ordered lab testing revealed the presence of Hep A antibodies in R.P.'s system. Tr. at 129. Upon further questioning, however, Dr. Shapiro acknowledged that he considered a Hep A etiology for R.P.'s TM in his initial assessment, though he later determined the relevant testing suggested the antibody response was evidence of a resolved infection. *Id.* at 171-72. Respondent otherwise does not assert any theory related to Hep A exposure.

not, however, identify which vaccine was implicated or why (in this case) R.P.'s immune cells targeted the spinal cord. *Id.* at 134, 137.[23]

Dr. Shapiro agreed with the mechanism[24] offered by Dr. Kinsbourne, which he described as an acute, innate immune reaction to vaccination "that caused [a] release of proinflammatory cytokines" resulting in immune system dysregulation (including demyelination and nerve/tissue damage). Tr. at 134-36, 309, 312-13; First Shapiro Rep. at 2.[25] Consistent with Dr. Kinsbourne, Dr. Shapiro identified the IL-6 cytokine as the primary destructive culprit in R.P.'s case (though he felt others could also play a role). Tr. at 137, 156; Second Shapiro Rep. at 2. He similarly maintained that cells in the immune system require some trigger to induce the production of the IL-6 cytokine (for example, an antecedent infection, or in his opinion, a vaccination). Tr. at 155. Dr. Shapiro allowed for the possibility that isotype variance, environmental, or genetic factors could also play a role. *Id.* at 136; Second Shapiro Rep. at 3.[26]

Consistent with Dr. Kinsbourne's testimony, Dr. Shapiro referenced Kaplin I in support of Petitioners' theory implicating the IL-6 cytokine as the likely destructive mediator of R.P.'s TM. Tr. at 319. Dr. Shapiro agreed that relevant testing conducted in Kaplin I revealed an onset of weakness and demyelination following direct injection of high levels of the IL-6 cytokine into rat spinal cords. *Id.* In his view, such experimental results were enough to show a "possible" connection between the upregulation of IL-6 and disease onset. *Id.* at 319-20. He further explained that in "a real world" cytokine-mediated reaction, many inflammatory cytokines are transmitted throughout the body at much faster pace. *Id.* at 319. He therefore deemed it reasonable to assume (based on Kaplin I) that since IL-6 (albeit in high levels) could initiate a demyelinating process in

[23] Dr. Shapiro's expert report filed in support of Petitioners' claim affirmed the above statement, but also made some reference to immune cells being "highly activated" due to stimulation by "multiple vaccines with adjuvants." First Shapiro Rep. at 3. It does not appear that he relied on this argument to the same extent at hearing.

[24] Though Dr. Shapiro appeared to agree with cytokine-mediated theory offered by Dr. Kinsbourne, at times during the hearing, he referred to R.P.'s reaction being consistent with a "hypersensitivity reaction" (or an antigen-antibody immune complex theory) which he described as activating "complement" and resulting in tissue damage. Tr. at 133. He also references hypersensitivity in the context of an acute, innate immune response. *Id.* at 134, 142. Apart from the above references, Dr. Shapiro's testimony regarding this type of reaction was vague and unclear. Notably, his expert reports filed in support of this matter offer no opinion regarding this theory and he filed no literature addressing the topic.

[25] At hearing, Dr. Shapiro at times referred to this cytokine-mediated attack as a product of the *adaptive* immune system (which would be inconsistent with the opinion of Dr. Kinsbourne, as well as the relevant scientific literature filed in support). *See, e.g.*, Tr. at 141. Later in his testimony, however, it appears he corrected this mistake. *Id.* at 173-74. Dr. Kinsbourne, at times, also described Dr. Shapiro's statements as adaptive in nature. *Id.* at 344, 346.

[26] Similar to Dr. Kinsbourne, Dr. Shapiro specifically testified that he is not relying on an adaptive process, such as molecular mimicry, as a mechanism in this case (though, he later opined that molecular mimicry could work had the timing of R.P.'s alleged reaction been more delayed). Tr. at 148, 174, 309, 313. He thus categorized R.P.'s reaction as "autoinflammatory[,]" rather than autoimmune. *Id.* at 148, 176, 178.

rats, IL-6 alone (or in combination with other inflammatory cytokines) could result in the same process in humans. *Id.*

Dr. Shapiro also relied heavily on the initial fever and irritability documented in R.P.'s hospitalization records as evidence that R.P. was experiencing an overproduction of cytokines. Tr. at 175, 323-34; Second Shapiro Rep. at 1-2. At hearing, Dr. Shapiro noted that R.P. presented with a fever of 100.2 at his January 9th ER visit (though, this was lower than would ordinarily be deemed concerning). Tr. at 323 ("we worry about fevers over 101"). In his view, a "low grade" fever could be attributable to a recent vaccination. *Id.* at 324.

Also consistent with Dr. Kinsbourne, Dr. Shapiro referenced Kashiwagi in support of his assertion that vaccines stimulate the production of proinflammatory cytokines (as evidenced by fever). Tr. at 316-17. Dr. Shapiro emphasized that researchers in Kashiwagi found that the G-CSF cytokine was elevated in the peripheral blood of patients concurrently stimulated with the DPT, Hib, and PCV7 vaccines. *Id.* at 317; Kashiwagi at 1. He similarly noted that higher levels of G-CSF were observed in febrile patients (as opposed to nonfebrile participants). Tr. at 317; Kashiwagi at 1. Given the above, Dr. Shapiro found it reasonable to theorize that R.P.'s fever was caused by the G-CSF cytokine and others (and thus occurred in response to his recent vaccination). Tr. at 318. Notably, however, Dr. Shapiro did not address the fact that Kashiwagi found no increase in the *IL-6 cytokine* in the peripheral blood of the patients tested. He also otherwise acknowledged that R.P.'s cytokine levels were never tested in connection with his onset of TM – making it impossible herein to corroborate the theoretical contention of what an overproduction of those cytokines could do. *Id.* at 175, 318.

Besides the above, Dr. Shapiro placed great significance on the elevated neutrophil levels noted in R.P.'s record from his hospitalization testing as evidence of an adverse innate response to his vaccinations. Tr. at 131, 135, 141, 314. Dr. Shapiro defined neutrophils as "complement proteins" released by the body during an immune reaction. *Id.* at 145. According to Dr. Shapiro, neutrophils draw in immune cells (or "scavengers") via chemotaxis to fight off whatever agent (usually an infection) is triggering the response. *Id.* at 145, 328. Neutrophils are initially released within 24 hours following a triggering agent, whereas lymphocytes (or the secondary responders) typically take over within a 24-48 period thereafter. *Id.* at 146. Both proteins can be drawn out (or produced) by various agents in the context of TM (including direct injury to the spinal cord or viral infection of the spinal cord). *Id.* at 145-45, 328.[27]

[27] On rebuttal, Dr. Kinsbourne generally affirmed the points made by Dr. Shapiro regarding the neutrophilic evidence in R.P.'s record. *See* Tr. at 352 (categorizing neutrophils as part of the initial response mounted by the innate system and lymphocytes as adaptive responders), 359 (arguing elevated neutrophils are evidence of a proinflammatory cytokine reaction to a vaccine), 363 (increased neutrophils are evidence of a close-in-time trigger). He offered no literature to support these statements, however. And it appears he mainly relied on and reiterated the statements made by Dr. Shapiro (as described above).

In his opinion, the release of proinflammatory cytokines (including IL-6) into the blood stream can cause not only a breach of the BBB (and resulting inflammatory response), but also an increase in neutrophil production. Tr. at 135, 175, 314. In the present matter, R.P.'s lab results at the time of his TM diagnosis evidenced 87 percent neutrophils in the spinal fluid. *Id.* at 131 (citing Ex. 5 at 17). Accordingly, Dr. Shapiro asserted that the neutrophilic accumulation in the CSF not only revealed underlying inflammation in the spinal cord, but supported his contention that R.P.'s underlying disease had been initiated by an acute trigger (or event close-in-time to the relevant testing/disease presentation).[28] *Id.* at 142, 147 ("within a few days"). Accordingly, Dr. Shapiro opined that evidence of increased neutrophils (or the immune system's "immediate response team") suggested the existence of an innate response (as they migrate to the site of the injury and accumulate within a 24 to 48 period to protect against the ensuing damage). *Id.* at 146. In contrast, an infection three weeks prior to onset of injury (in this case, TM) would not initiate a production of neutrophils in the CSF (but would rather initiate the production of secondary lymphocytes). *Id.* at 146-47, 311.[29] Despite the above, however, Dr. Shapiro did not address how (if at all) the increased neutrophils could be specific indicia of a disease process such as TM.[30]

As independent support for his contentions about the evidentiary significance of neutrophils, Dr. Shapiro offered one item of literature. Tr. at 315-16; *see* S. Matas, et al., *Cerebrospinal Fluid Analysis in the Context of CNS Demyelinating Diseases*, 72 Arq. Neuropsiquiatr. 685 (2013), filed as Ex. 77 (ECF No. 81-1) (originally published in Spanish journal) ("Matas"). Matas discusses the differences in CSF content analyses for three CNS demyelinating conditions: acute demyelinating encephalomyelitis ("ADEM"), multiple sclerosis ("MS"), and neuromyelitis optica ("NMO"). *Id.* at 685. In considering the CSF of 687 patients presenting with one of these demyelinating diseases, Mata determined that each typically contained a "mixture of cells" – inconsistent with R.P.'s neutrophil-predominant readings, especially since he was not believed to have been experiencing a bacterial infectious process at the time. Tr. at 315; *see* Matas at 687. Accordingly, in Dr. Shapiro's view "some other mechanism" (i.e. R.P.'s January 2013 vaccinations) was likely responsible for the influx of neutrophils. Tr. at 315. Matas *does* support the assertion that the CSF of patients with demyelinating disease can

[28] Notably (and consistent with his inadvertent confusing of innate and adaptive), Dr. Shapiro initially described the production of neutrophils as consistent with an *adaptive* response. Tr. at 147-48. He later corrected this statement. *Id.* at 311 (noting neutrophilic accumulation is consistent with an innate response).

[29] According to Dr. Shapiro, lymphocytes in CSF would be more typical of delayed trigger in the context of TM (for example, an antecedent viral infection). Tr. at 144, 314-15.

[30] As noted earlier, Dr. Shapiro also at times contradicted the above theory at hearing. For example, at one point, he asserted that neutrophils were produced in the adaptive immune system. Tr. at 148. He also testified that the resulting spinal inflammation R.P. experienced was due to inflammatory tissue damage as opposed to an attack with an "autoimmune" basis. *Id.* He then later opined that the facts of R.P.'s case did not suggest an autoimmune response occurred (which would be consistent with the overall theory offered by Petitioners: that R.P. experienced a cytokine-mediated attack). *Id.* at 148-49.

evidence a variety of cells (including neutrophils, macrophages, eosinophils, lymphocytes, and/or plasma cells), but does *not* discuss the CSF of TM patients specifically, and it does *not* contain any conclusions about what a neutrophil-predominant CSF suggests in terms of identifying an illness's etiology (as opposed to other CSF findings like specific antibodies). *See* Matas at 687.

Dr. Shapiro next discussed the reasonableness of the timeframe for R.P.'s symptom onset. Tr. at 158. Based on his review of the record, Dr. Shapiro opined that R.P.'s onset of TM symptoms occurred within 24 to 48 hours following vaccine administration (which would be somewhat sooner than that opined to by Dr. Kinsbourne). *Id.* at 134. At times, however, Dr. Shapiro seemed to embrace one end of his proposed time frame over the other. *See, e.g., id.* at 133, 134 ("within 24 hours he did have some symptoms and within 48 he had tissue damage"), 144 (R.P. "developed symptoms within 24 hours . . . and had a continuous progressive course"), 137 (asserting R.P. experienced fever caused by IL-6 cytokine production); *but see id.* at 157-58, 312-13 (agreeing with the two-day timeframe with peak cytokine production at 24 hours); First Shapiro Rep. at 4 (suggesting R.P. developed symptoms at 36 hours).

To support his onset timing, Dr. Shapiro explained that proinflammatory cytokines in the body are released four to six hours following stimulation. Tr. at 158. In his opinion, the body can produce enough cytokines within a day to produce irritability, fatigue, and fever (and did so in R.P.'s case), which would be consistent with a 24-hour onset. *Id.* Spinal inflammation, however, would then occur within an additional 24-hour period, subsequently resulting in a full TM course. *Id.* In support of his timeframe determination, Dr. Shapiro referenced many of the same case reports cited earlier by Dr. Kinsbourne. Tr. at 159-60; Second Shapiro Rep. at 2; *see also* Agmon-Levin at 1200; Kaplin II at 4; H. Topalogu, et al., *Optic Neuritis and Myelitis After Booster Tetanus Toxoid Vaccination*, 339 Lancet 178, 178 (1992), filed as Ex. 55 (ECF No. 73-7). He also referenced a case report which detailed an onset of redness and swelling at the vaccine injection site 12 to 28 hours following receipt of the pneumovax vaccine. Tr. at 157; Second Shapiro Rep. at 2 (noting the case report was dated in 2015 and not filed, but taken from his practice's "personal archives"). Dr. Shapiro otherwise suggested that Kaplin I's rat model supported his point (as rats receiving a direct injection of IL-6 into the spinal cord developed an onset of weakness over two days). Second Shapiro Rep. at 3.

Similar to Dr. Kinsbourne, Dr. Shapiro also offered an opinion contending that R.P.'s rapid onset could be a product of a reaction due to R.P. being presensitized by his previous vaccinations (presumably the two previous DTaP vaccinations he had received in his life, which would cause "pre-existing sensitized effector cells" to be activated upon re-exposure to the vaccination), though at hearing he seemed to walk back this assertion. First Shapiro Rep. at 4; Tr. at 128 ("I'm not sure the evidence supports that basis"). He also filed no literature addressing this argument. First Shapiro Rep. at 4. At hearing, Dr. Shapiro also opined that the immaturity of an infant's BBB supported Petitioners' contention that R.P.'s TM symptom onset could occur more quickly (or

within two days following vaccination). Tr. at 137 (the BBB is "a lot more permeable, and it's not as intact as it is later in life"). He did not, however, offer literature discussing the topic, and his reports similarly did not mention this point.

Dr. Shapiro next attempted to refute Respondent's contention that R.P.'s TM had been triggered by a pre-existing viral illness in December 2012. Tr. at 144-45, 150-53, 320; First Shapiro Rep. at 3, 5. Rather, other than the fact that R.P. was diagnosed with a URI, R.P.'s medical record offered an inconclusive picture. Tr. at 152-53. Dr. Shapiro agreed that R.P.'s health history evidenced some mild respiratory symptoms (and serous otitis media) roughly three to four weeks prior to his onset of TM, but maintained that it was not necessarily viral in nature (and in particular that the serous form of an ear infection was not viral either). *Id.* at 153; Second Shapiro Rep. at 1; *see* K. Hayes, *Serous Otitis Media: Fluid in the Ears*, Very Well Health, https://www.verywellhealth.com/serous-otitis-media-1192111?print (last updated Aug. 2017), filed as Ex. 75 (ECF No. 73-8) ("serous otitis media is not an ear infection"). There was otherwise no evidence of a fever or severe, infectious symptoms in the December 2012 pediatric note. Tr. at 153; Ex 8 at 31. He also referenced MRI evidence taken during that time, which he opined showed evidence of sinus thickening as "nonspecific" or "mild mucosal swelling." Tr. at 160.[31] He thus categorized these earlier symptoms as nonspecific at best, or possibly related to teething. *Id.* at 150.[32] Overall, he concluded that the December 2012 record did not support an identified, definite virus or infection as the triggering event. *Id.*[33] Though, he agreed on rebuttal (and in his report) that respiratory viruses could trigger an adverse immune response resulting in TM. *Id.* at 322; First Shapiro Rep. at 3; Second Shapiro Rep. at 1.

Dr. Shapiro also found R.P.'s lab tests results to be supportive of this point. As noted earlier, Dr. Shapiro emphasized that R.P.'s viral panel conducted during his hospitalization was negative for any infectious agent. Tr. at 152. Had R.P. experienced a viral-induced TM, R.P.'s clinical presentation (including labs) would have identified the specific viral trigger. *Id.* at 150-51. He also suggested a prior infection would have triggered the production of lymphocytes (which R.P.'s labs similarly did not reveal). *Id.* at 144, 150, 153. Overall, he asserted that a post-infectious CNS event would have included both documented viral symptoms post-vaccination, and/or

[31] Petitioners filed the Nazari article in support of these particular assertions. *See* M. Nazari, et al., *Incidental Detection of Sinus Mucosal Abnormalities on CT and MRI Imaging of the Head*, 3 Quant. Imaging Med. Surg. 82 (2013), filed as Ex. 78 (ECF No. 81-2).

[32] *See* S. Wilson, et al., *Tooth Eruption and Otitis Media: Are They Related?*, 8 Am. Acad. Pediatric Dentistry 296, 296 (1986), filed as Ex. 42 (ECF No. 72-2);

[33] Upon further questioning, he also asserted that a viral URI was not one of the typical viruses associated with an onset of TM. Second Shapiro Rep. at 1. Rather, he limited the TM viral triggers to include only varicella zoster, herpes simplex, cytomegalovirus, Epstein-Barr, influenza, echovirus, HIV, Hep A, and rubella. *Id.*; *see Transverse Myelitis Fact Sheet*, NIH, filed as Ex. 47 (ECF No.72-7).

mediation by a clearly identifiable antibody or lymphocyte (both of which were not definitively supported by R.P.'s record). *Id.* at 152, 322.

D. *Dr. Timothy Lotze*

Respondent submitted one report from Dr. Lotze, who also testified for Respondent at hearing. *See* Expert Report, dated July 10, 2014 (filed as Ex. A) (ECF No. 27-1) ("Lotze Rep.").

Dr. Lotze obtained his bachelor's degree from Texas A & M University in College Station, Texas, followed by a medical degree at the University of Texas, San Antonio. Lotze CV, filed as Ex. C (ECF No. 32-1) ("Lotze CV") at 1. Thereafter, he completed two residencies and an internship at Ohio State University in Columbus, Ohio, finishing his education with a residency in child neurology at Baylor College of Medicine in Waco, Texas. Tr. at 178. He was then hired as a faculty member at the Baylor College of Medicine, where is currently employed as an associate professor of pediatrics and child neurology. *Id.*; Lotze CV at 1. He also serves as the director for pediatric multiple sclerosis at Texas Children's Hospital, as well as the director of the Muscular Dystrophy Association Care Center (both in a clinical setting). Tr. at 179. He is board certified in both neurology and pediatrics. Lotze CV at 1-2.

Dr. Lotze testified that he spends fifty percent of his time treating patients. Tr. at 179. At Texas Children's, Dr. Lotze treats infants and pediatric patients with both neuromuscular disease and demyelinating CNS syndromes (including ADEM, MS, and NMO). *Id.* He estimated that he has diagnosed around 100 children with TM over the course of his practice. *Id.* Dr. Lotze serves as a panel reviewer for multiple scientific journals (including the *Journal of Pediatrics* and the *Journal of Neurology*). Lotze CV at 3. He has also published papers on various CNS disorders (including TM, MS and NMO). *Id.* at 3-7.

Although Dr. Lotze acknowledged that he lacked specific training or expertise in immunologic matters, he opined that R.P.'s TM was not related to any of the vaccinations he received in January 2013. Tr. at 182, 196; Lotze Rep. at 4. Based on his review of the record, Dr. Lotze argued instead that R.P.'s TM-related symptoms presented within 24 hours of vaccine administration, making it unlikely that the vaccines at issue herein were causative of his condition. Lotze Rep. at 5. He also suggested that R.P.'s condition could be attributable to a pre-existing URI. *Id.*

Consistent with Petitioners' experts, Dr. Lotze characterized TM as an inflammatory process damaging the spinal cord's myelin (or insulation surround the nerve), which causes demyelination and destruction of nerve tissue, resulting in both motor and sensory dysfunction. Tr. at 183; Lotze Rep. at 4; *see* V. Wolf et al., *Pediatric Acute Transverse Myelitis Overview and Differential Diagnosis*, 27 J. Child Neurol. 1426, 1426 (2012), filed as Ex. A, Tab 1 (ECF No. 70-1) ("Wolf"). The clinical symptoms of TM can include weakness, lack of or loss of muscle tone (resulting in flaccid paraplegia), lack of sensation, pain, irritability, bladder dysfunction or

complete absence of bladder activity, and/or bowel issues. Tr. at 183-84; Lotze Rep. at 4; Wolf at 1428.

Dr. Lotze testified that a child with acute onset TM would likely present with symptoms such as general lethargy, lack of motor ability, pain, or sensory deficits (similar to the typical course described above). Tr. at 184; *see also* Wolf at 1428. It could, however, be difficult to evaluate the presenting symptoms in an infant given their inability to voice specific concerns. *Id.* at 185; Lotze Rep. at 4. In assessing an infant for TM, Dr. Lotze opined that a "clear change" in the child's neurological abilities (such as an inability to sit up, be picked up, or changes in bladder function) would indicate that an adverse process was occurring. Tr. at 185. With infants, many times treaters will develop differential diagnoses when considering TM (given the constellation of symptoms that can present as well as the infant's inability to describe them). *Id.*

As Dr. Lotze explained, a TM diagnosis involves both the patient's clinical history and ancillary diagnostic studies, such as an MRI and CSF testing. Tr. at 183. Despite some well-defined diagnostic criteria, the cause of TM is typically unknown (i.e. idiopathic). *Id.* at 189-90; Lotze Rep. at 4. However, TM can be "disease-related" in some circumstances, meaning onset coincides with another disease process (for example, MS, NMO, or lupus), some of which can be verified through relevant antibody testing. Tr. at 190. He also allowed for the conclusion that TM can be initiated by a viral illness. *Id.* at 192; Lotze Rep. at 4 (noting 50-100% of pediatric TM cases are preceded by a mild URI three to four weeks prior to acute presentation). More often than not, however, Dr. Lotze testified that TM is overwhelmingly idiopathic in nature, with no diagnostic lab test which can identify a trigger. Tr. at 189-90.

Based on his own review of the medical records, Dr. Lotze agreed that R.P. was properly diagnosed with TM based on the MRI evidence (which confirmed a "very extensive inflammatory process" in the spinal cord from the cervical to thoracic region) along with the CSF analysis conducted during his hospital stay. Tr. at 188-89; Lotze Rep. at 4. Contrary to Petitioners' experts (who attributed R.P.'s onset of TM to his vaccinations), however, Dr. Lotze concluded that R.P.'s TM was instead more likely idiopathic in nature (given that immediate treaters could not identify a possible cause at the time of diagnosis). Tr. at 189, 191-92. He acknowledged that later-in-time treaters considered the vaccine as playing some role, but maintained that a "direct cause" was not clearly identified during R.P.'s hospital stay in light of the relevant testing conducted at that point. *Id.* at 192, 204-05.

R.P.'s respiratory symptoms pre-vaccination, Dr. Lotze proposed, could have played some role in his development of TM. Tr. at 197; Lotze Rep. at 4-5. In so arguing, Dr. Lotze relied primarily on two medical evaluations R.P. received during his hospitalization in January 2013. Tr. at 192. That record assessed R.P. with "acute transverse myelitis" following a "viral illness." *Id.* (citing Ex. 5 at 18-24). Dr. Lotze agreed, however, that R.P.'s viral and bacterial panels conducted during his hospitalization were both negative. *Id.* He also cited to various pieces of literature and his own clinical experience in opining that the "vast majority" of idiopathic TM patients will have

reported some form of an upper respiratory infection prior in the weeks preceding onset of clinical symptoms. *Id.* at 190; Lotze Rep. at 5; *see also* Wolf at 1427 (pediatric acute TM is preceded by a "mild illness" in the three weeks prior in 50 to 100 percent of reported cases). Dr. Lotze also noted that multiple case reports filed by Petitioners (reporting an onset of TM post-vaccination) involved a preexisting viral illness or respiratory symptoms. Tr. at 190 (citing Riel-Romero at 688; Whittle at 1450). Apart from the above, Dr. Lotze could not firmly identify a cause of R.P.'s TM, nor was he aware of any association between TM and vaccination as set forth in any medical or scientific literature. *Id.* at 206, 223-24.

As to the timing prong, Dr. Lotze testified that R.P.'s onset of TM symptoms likely occurred on January 8th (or around 24 hours following vaccination), given the symptoms documented in the record (including fever, urinary retention, generalized weakness, and irritability). Tr. at 186, 187-88, 207, 211. In particular, Dr. Lotze referenced records from R.P.'s initial hospital presentation on the 8th which revealed concern for urinary retention, generalized weakness, and pain (i.e. not wanting to be picked up or touched) throughout the day of January 8th. Tr. at 187, 198; Lotze Rep. at 4-5. Dr. Lotze acknowledged that notes from the visit indicated a normal neurologic assessment,[34] but he also took note of the fact the R.P.'s parents and reported persistent weakness (and urinary retention) with onset of January 8th (at daycare), along with a low-grade fever within hours following vaccine administration. Tr. at 187-88, 200, 202-03; Lotze Rep. at 5. The normal neurologic exam did not change Dr. Lotze's opinion (even if tone and power were not considered). Tr. at 207.

Given the evolution of R.P.'s symptoms, Dr. Lotze agreed that the continuing low-grade fever and irritability reported in the early morning of January 8th would be consistent with a TM course (as well as a post-vaccination reaction). Tr. at 187, 203. Even if R.P. lacked "full manifestations" of TM symptoms on the 8th, Dr. Lotze did not deem his initial symptoms to be significantly different in nature from those documented at the time of diagnosis on January 9th. *Id.* at 187, 198, 208. Overall, Dr. Lotze stressed that his onset opinion considered the whole picture with regard to R.P.'s health course (including both visit notes on January 8th and 9th, along with parental reports of symptoms), which in his view evidenced a progression of symptoms with onset on January 8th. *Id.* at 200. Based on his determination that onset occurred closer-in-time to January 8th, Dr. Lotze opined that the vaccinations R.P. received could not be the inciting factor for his TM given how rapidly his symptoms progressed to diagnosis from date of vaccination. *Id.*

Given Petitioners' reliance on the neutrophilic evidence contained in R.P.'s records (and as evidence of a vaccine injury), Dr. Lotze offered some testimony in an attempt to diminish its significance. Dr. Lotze agreed that increased levels of neutrophils can be detected in the CSF early

[34] At hearing, Dr. Lotze pointed out that the "neurologic exam" conducted on January 8th was performed by an ER physician. Tr. at 187, 198, 210. But in his opinion, it was possible that this physician did not conduct a full assessment of neurologic symptoms at this original presentation. *Id.* Dr. Lotze also later noted that R.P. was not seen by a neurologist until January 10th. *Id.* at 210.

on in a TM diagnosis, while protein production tends to shift to "lymphocytic predominance" later on in the disease process if the CSF is retested (which usually does not occur). Tr. at 195-96. But he maintained that Petitioners' experts had not adequately explained *why* neutrophils were produced in the early stages of TM as opposed to in the context of other immune responses. *Id.* at 222. According to Dr. Lotze, the production of neutrophils and lymphocytes are a normal response to *any* autoinflammatory process (whether caused by a virus or an infection). *Id.* at 196, 217-18, 221.[35] In R.P.'s case, Dr. Lotze acknowledged that the record indicated a neutrophilic percentage of 87% (with a contrasting lymphocytic percentage of 3%), but he concluded this *only* indicated a neutrophilic predominance – not proof of cytokine involvement or vaccine-causation consistent with Petitioners' theory. *Id.* at 216-18.

Dr. Lotze did not offer any testimony regarding Petitioners' proposed causation mechanism in this case. He readily admitted that he is not an immunologist and could not offer an opinion regarding the relationship between vaccine administration and a pathologic process resulting from the stimulation of proinflammatory cytokines. Tr. at 215. Even so, he maintained (based on his clinical experience) that he could find no "biological evidence for causation" in light of the facts contained in R.P.'s medical history. *Id.* at 206.

E. *Dr. Christine McCusker*

Dr. McCusker served as Respondent's second expert. She submitted two expert reports and testified at hearing *See* Expert Report, dated June 25, 2014, 2016, filed as Ex. B (ECF No. 27-2) ("First McCusker Rep."); Expert Report, dated Aug. 24, 2015, filed as Ex. E (ECF No. 40-1) ("Second McCusker Rep.").

Dr. McCusker received her Masters in Molecular Virology in 1988, followed by a medical degree in 1993, from McMaster University in Hamilton, Ontario. McCusker CV, filed as Ex. D (ECF No. 32-2) ("McCusker CV") at 1; Tr. at 226. She completed her residency in pediatrics at Montreal Children's Hospital, McGill University ("McGill"). Tr. at 227. Dr. McCusker also completed a fellowship in allergy and immunology at McGill. *Id.* She currently serves as an associate professor of pediatrics at McGill University Health Centers and directs the translational respiratory research disease unit. *Id.* at 227-28. Her research domain also includes a wet lab centered on understanding the interplay between the innate and adaptive immune system. *Id.* at 230-31. Dr. McCusker estimated that she spends fifty percent of her time in a research/teaching/administrative capacity. *Id.* at 228. She is licensed in Canada and holds a certification from the Royal College of Physicians and Surgeons of Canada in pediatrics and clinical immunology. *Id.* at 227.

[35] Dr. Lotze also cites to a visit note authored by R.P.'s treating infectious disease physician confirming this point. Tr. at 221 (citing Ex. 5 at 21).

Dr. McCusker also maintains a clinical practice. She is an allergist "in practice" and routinely sees infant and pediatric patients within the allergy/immunology and general pediatric clinics at McGill. Tr. at 228. She also works part-time as an urgent care physician at Montreal Children's Hospital. *Id.* In her immunology practice, Dr. McCusker treats patients with various allergic diseases (including allergies to vaccinations). *Id.* at 229. She is also responsible for diagnosing and managing primary and secondary immunodeficiencies. *Id.* at 229-30. Dr. McCusker's treatment responsibilities in the general pediatric clinic are more varied and can include acute care of small injuries or more serious ailments (i.e. a brain tumor or demyelinating disease). *Id.* at 230, 307. At hearing, Dr. McCusker estimated that she has treated roughly four patients with pediatric TM over the course of her career. *Id.* at 307.

Consistent with Petitioners' experts, Dr. McCusker agreed that R.P. was properly diagnosed with TM close-in-time to his January 2013 vaccinations. First McCusker Rep. at 7. She opined, however, that the vaccines played no causal role in its development. Tr. at 234. In particular, Dr. McCusker took issue with certain components of Petitioners' proposed immunologic mechanism—a cytokine storm resulting in dysregulation of the innate immune system—arguing that the facts of this case (coupled with the relevant medical and scientific literature) did not provide a reliable explanation for how cytokine upregulation *could* lead to a pathologic process resulting in TM within the timeframe proposed.

Dr. McCusker began her testimony by describing idiopathic TM and its possible causes. Consistent with prior testimony offered in this case, she categorized TM as a "progressive inflammatory disease" of the spinal cord brought about by an inappropriate immune response directed against self structures in the body. Tr. at 245, 285; First McCusker Rep. at 2. Medical science, however, has not conclusively determined the cause of idiopathic TM. Tr. at 245, 276. In her view, most of what is known about the disease relates to a patient's course only *after* the disease has been initiated (i.e. symptomology, cytokine levels, etc.). *Id.* at 276. She acknowledged that the relevant research on the disease supports the conclusion that viral infections (via an autoimmune theory) or direct trauma to the spinal cord can result in an onset of TM. *Id.* at 244, 279; First McCusker Rep. at 2-3. Thus, in the specific context of a known autoimmune cause,[36] Dr. McCusker theorized that "autoreactive components" directed against the myelin or spinal cord could be a product of a T cell-mediated response against the self-molecules. Tr. at 246.

Dr. McCusker next discussed her own understanding of Petitioners' proffered causation theory.[37] According to Dr. McCusker, the sequence of events necessary for TM to develop post-

[36] *See* Y. Katz-Levy, et al., T*emporal Development of Autoreactive Th1 Responses and Endogenous Presentation of Self Myelin Epitopes by Central Nervous Systems-Resident APCS in Theiler's Virus Infected Mice*, 165 J. Immunol. 304 (2000), filed as Ex. B, Tab 5 (ECF No. 70-8) (filed to support the mechanisms by which an infectious agent could trigger an autoimmune disease).

[37] Dr. McCusker expressed some confusion at hearing regarding portions of Dr. Shapiro's testimony as it related to

vaccination (in R.P's case) would require *first* the activation of the immune cells by proinflammatory cytokines (specifically IL-6), followed by bulk cytokine migration from the periphery through the BBB. First McCusker Rep. at 7. Then signaling for the inflammation to begin in the spinal cord would have to occur (in conjunction with activation of inflammatory cells), along with migration of immune cells to this site of injury. *Id.* In addition, the TM-related inflammation and demyelination would have to *precede* the development of any symptomology (resulting in an onset of observable symptoms over a period of days rather than hours). *Id.* As discussed in more detail below, Dr. McCusker identified multiple deficiencies with this theory.

Dr. McCusker defined cytokines as a complex system of "proteins" released by immune cells during an innate immune response. Tr. at 236. She estimated that cells can produce between 60-70 different types of cytokines, all with various cellular targets and functions (depending on their location in the body). *Id.* at 237-38. For example, the body can produce "growth factor" cytokines during an immune response. *Id.* at 237. Growth factor cytokines, such as IL-2, act as signaling molecules that encourage T cell growth. *Id.* "Proinflammatory" or pyrogenic cytokines, on the other hand, are released immediately (and increased) during periods of existing inflammation and induce other cells to combat injury, infection, and the presence of disease. *Id.* at 237, 252, 292-93; First McCusker Rep. at 4. Cytokines are primarily a result of activation of the innate immune system, and can also implicate the development of "sickness factors" (such as general malaise or irritability) upon initial stimulation. *Id.* at 282, 291-92. Dr. McCusker identified the "classic" proinflammatory cytokines as IL-1, IL-6, and TNF alpha. *Id.* at 282.

According to Dr. McCusker, cytokine-mediated inflammation caused by an innate immune response to a vaccine is typically specific or localized to the place of insult (for example redness, pain, or swelling at the injection site). Tr. at 249.[38] She agreed that inflammation can expand within the body, but it would do so locally (not systemically). *Id.* at 249-50. In R.P.'s case, for example, Dr. McCusker postulated that a vaccination received in the thigh could cause inflammation at or around the thigh area, but not the type of inflammation that could spread to other organ systems in the body. *Id.* She agreed also that a localized response to a vaccination could also cause fever or

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the proffered medical theory in this case. As she understood it, Petitioners' theory centered on a vaccine-induced production of proinflammatory cytokines (which caused an activation/dysregulation of the innate immune system and eventually resulted in inflammation in the spinal cord). Tr. at 234. At times, however, Dr. Shapiro seemed to describe Petitioners' theory as a "type III hypersensitivity reaction" or an immune complex disease. *Id.* Dr. McCusker opined that a type III hypersensitivity reaction requires the presence of "preformed mediators" or antibodies that bind to antigens and result in immune complex deposits. *Id.* at 235. The amplified immune responses is then a result of the preformed immune complexes, not cytokines. *Id.* Thus, she found that kind of theory wholly inapplicable to the present matter.

[38] Dr. McCusker agreed that adjuvants can upregulate inflammation to assist with an immune response. Tr. at 254. She maintained, however, that such upregulation would *only* result in a more amplified localized reaction (consistent with the above). *Id.* In her view, adjuvants play no role in any alleged cytokine upregulation or expansion to the CNS. *Id.* at 255-56. She also cited literature generally discussing the safety of using adjuvants in vaccines. *See* M. Kool, et al., *Alum Adjuvant Boosts Adaptive Immunity by Inducing Uric Acid and Activating Inflammatory Dendritic Cells*, 205 JEM 869 (2008), filed as Ex. E, Tab 3 (ECF No. 71-5).

sickness behaviors (as noted earlier). *Id.* a 291-92. But these symptoms are not due to systematic circulation of cytokines, but "local stimulation of nerve endings resulting in a signal directly to the hypothalamus." *Id.* at 292.

Consistent with the above, Dr. McCusker categorized the proinflammatory cytokine, IL-6, as "primarily a localized cytokine" produced in the periphery. Tr. at 238-39. In the immune system, IL-6 is released in very low levels in the systemic circulation during an inflammatory process (as evidenced by the onset of fever and inflammation). *Id.* at 238; First McCusker Rep. at 4. In the CNS, or the brain, however, IL-6 can play a different role depending on the site of expression and timing of release (including the differentiation/survival of neuronal or glial cells, the amelioration of disease, and/or the regulation of food intake, energy expenditure, and body temperature control). Tr. at 238; First McCusker Rep. at 4. Brain cells can also express proinflammatory cytokines in response to an attack or infection in the brain or CNS. Tr. at 239; *see* M. Erta, et al., *Interleukin-6, A Major Cytokine in the Central Nervous System*, 8 Int. J. Bio. Sci. 1254, 1256 (2012), filed as Ex. B, Tab 3 (ECF No. 70-6) (finding both the central and peripheral nervous system can express IL-6).

Based on her review of the relevant scientific and medical literature filed in the present matter, Dr. McCusker disputed Petitioners' contentions that a vaccine could sufficiently stimulate the production of IL-6 to result in a pathogenic process leading to TM. Tr. at 243, 306. She began by referencing Kaplin I (which Petitioners argue supports the conclusion that an upregulation of IL-6 *alone* is sufficient to cause TM). Dr. McCusker agreed that Kaplin I supports the conclusion that IL-6 has been shown to be elevated in the CSF of TM patients – and more importantly, that it may mediate some of the immunopathological effects of the disease as well. Tr. at 294; First McCusker Rep. at 4; Kaplin I at 2733, 2738. But, she maintained, Kaplin I does not persuasively implicate any vaccine as a trigger for the IL-6 production in the first place. First McCusker Rep. at 4. Kaplin I also identified the likely source of the IL-6 production as the microglia located *inside* the spinal cord/CNS, not from the periphery as Petitioners propose. Tr. at 242; Kaplin I at 2733. The Graber study similarly undercuts the role of IL-6 by suggesting other soluble factors might be involved in its production in astrocytes. Graber at 130.

In addition, Dr. McCusker took issue with the rat model evidence in Kaplin I, noting that it resulted from the use of "super high" doses of IL-6 (in amounts exceeding that normally found in the human blood by multiples of thousands) injected directly into the spinal cord, thus bypassing the other biological processes that Petitioners' theory assumes to have occurred. Tr. at 242-43; *see* Kaplin I at 2735. She therefore maintained that Kaplin I only supported the argument that IL-6 *could* be implicated in the development of the pathology associated with the disease – not that vaccination could be causative of an overproduction of IL-6 originating in the periphery sufficient to cause CNS harm. Tr. at 243.

Dr. McCusker next discussed the relationship between the *alleged* vaccine-induced IL-6 cytokine upregulation and the eventual migration of these cytokines from the periphery through the BBB. First McCusker Rep. at 7. Dr. McCusker defined the BBB as both the "theoretical" and "actual" construct separating the periphery from the CNS. Tr. at 238-39. Breach of the BBB could occur via the "actual transport" of cytokines from outside the CNS through the BBB via the binding of cells at its surface, or through an "active transport system" involving cytokine/receptor signaling. *Id.* at 241. Dr. McCusker thus admitted that cytokines can cross the BBB, but opined that cytokines released in the periphery are produced in too small amounts to have a harmful CNS effect. *Id.* at 253, 267. She stressed that it could not be assumed that periphery cytokines cause every adverse event that occurs in the CNS (especially since, as noted above, cytokines can be expressed inside the CNS without peripheral involvement). *Id.* at 300. Dr. McCusker thus argued that the Petitioners could not explain *how* a miniscule amount of IL-6 (while originating in the periphery) could cross the BBB and expand to the CNS. *Id.* at 249-50, 296.

Dr. McCusker also supported her opinion with reference to Kashiwagi. Tr. at 265. She acknowledged that Kashiwagi supports the contention that *small* amounts of proinflammatory cytokines are upregulated upon receipt of a vaccination (and can lead to fever as well). *Id.* at 265, 267; Kashiwagi at 677. But Kashiwagi concluded that only one cytokine (G-CSF, a growth-factor cytokine) was found to be upregulated in febrile, vaccinated children (thus, in her view, *only* G-CSF could be a good marker for prediction of onset of fever). Tr. at 266. This conclusion undercut Petitioners' assertion that IL-6 is the key vaccine-induced cytokine (as Kashiwagi found no significant increase in IL-6 production post-vaccination). Kashiwagi at 679. Accordingly, in her view, Kashiwagi better supported the conclusion that most peripheral cytokines (apart from G-CSF) are *not* increased post-vaccination, and are not necessarily associated with post-vaccination fever either. Tr. at 267; *see* Kashiwagi at 680.

In addition, Dr. McCusker maintained that R.P.'s overall clinical picture was inconsistent with what is known about a typical cytokine-mediated reaction or syndrome. In her view, a cytokine-mediated pathologic event (consistent with Petitioners' theory) would result initially in identifiable symptoms either originating or occurring in the periphery (including headaches stimulated from the periphery, hypotension, and/or peripheral organ damage) *prior* to any CNS harm. Tr. at 253-54. This was consistent with the fact (as also argued by Petitioners) that cytokines are released from the site of vaccination immediately upon the vaccine's administration (and can result in certain autoinflammatory syndromes and/or sickness factors). *Id.* at 252, 298. Here, however, R.P.'s clinical picture was inconsistent with the above. *Id.* at 254. At most, R.P.'s record included initial concerns for fever and general malaise (which could be vaccine-related), but he then experienced initial CNS symptoms at least by 36 hours following vaccine administration – nothing like what Dr. McCusker would expect in a cytokine-mediated reaction beginning peripherally. *Id.* at 254, 283, 290.

Along those same lines, Dr. McCusker opined that any cytokine-mediated innate immune response would require anywhere from two to four days – measured from activation in the *spinal cord* (and not the date of vaccine administration) to the onset of clinical symptomology. Tr. at 251-52, 288; Second McCusker Rep. at 3. For support, Dr. McCusker again referenced the rat model studied in Kaplin I, which, following direct injection of IL-6 (at extremely high levels) into the spinal cord, required at minimum two days *more* before weakness developed – and this did not account for the time it would take for the cytokines in the periphery to breach the BBB first. Tr. at 251, 288. The two to four-day timeframe proffered in Kaplin I could not be used as a template for assessing the timeframe from vaccination to CNS harm. *Id.* at 288. And as a result, in Dr. McCusker's view, R.P.'s onset of TM likely could not have occurred within two days of vaccination, as Petitioners alleged. *See id.*[39]

Based on her review of R.P.'s illness course, Dr. McCusker opined that any the inflammatory process responsible for R.P.'s TM likely began *prior* to his January 7th vaccinations. Second McCusker Rep. at 3; *see* Tr. at 244, 257. In so maintaining, she placed his onset of TM symptoms close-in-time to his emergency room presentation on the evening of January 8th (or within 36 hours post-vaccination). Tr. at 263-64, 290. Any inciting event leading to R.P.'s onset of TM would have been initiated and likely progressed over several days *before* recognizable neurologic symptoms manifested. *Id.* at 264; Second McCusker Rep. at 3. In support, Dr. McCusker referenced R.P.'s ER presentation notes from January 8th (which included concerns for symptoms that looked neurologic in nature, as well as a recommendation that R.P. return should symptoms progress further, underscoring their significance). Tr. at 264, 258. She also relied on her own clinical practice in so opining. In her own ER experience, it was common for a pediatric TM patient to present to the ER initially (with irritability, fever, and/or "soft neurologic signs"), and return with additional/progressive symptoms later resulting in a TM diagnosis. *Id.* at 263-64.

Dr. McCusker did acknowledge that the two-day timeframe argued by Petitioners was at least partially consistent with some of the case reports filed by Petitioners in support. Tr. at 269. Based on her view of the case report evidence, she determined that R.P.'s timing would be the second earliest reported case to date. *Id.* However, she directly disputed the significance of case reports as implicating any causal connection between a vaccine and an injury. *Id.* In her view, case reports simply alert the medical community to a *possible* association, to encourage further investigation. *Id.* at 268. She otherwise filed case reports in response reporting a vaccination close-in-time to onset of TM (but with onset measured by days rather than hours). *See, e.g.*, H. Kelly, *Evidence for Causal Association Between Oral Polio Vaccine and Transverse Myelitis: A Case History and Review of the Literature*, 42 J. Ped. & Child Health 155 (2006), filed as Ex. B, Tab 7

[39] At hearing, Dr. McCusker testified that she would not accept Petitioners' cytokine-mediated theory even if R.P.'s TM onset occurred *six* days following administration – a period of time more consistent with her reading of Kaplin I. Tr. at 296-97. Given the way cytokines are regulated in the immune system (i.e. produced locally), by day six, the periphery would contain insufficient cytokines left over from the initial inciting event to keep up the pathologic process implicated in such a theory. *Id.* at 297-98.

(ECF No. 71-2) (six-month-old infant developed TM seven days following receipt of oral polio vaccine); G. Zanoni, et al., *Transverse Myelitis After Vaccination*, 9 Eur. J. Nephrology 687 (2002), filed as Ex. B, Tab 6 (ECF No. 71-1) (fifteen-month-old infant developed TM twenty-one days following receipt of MMR vaccine).

Dr. McCusker also directly disputed Petitioners' reliance on Netea to support the contention that R.P.'s previous vaccine doses could have hastened his onset of TM symptoms via a presensitization/anamnestic response. Tr. at 247-48. Based on her review of Netea and her knowledge of general immunologic principles, Dr. McCusker opined that the purpose of a booster vaccination is to increase an immune response to certain components of the vaccine by training the immune system's memory B/T cells to recognize the invader. *Id.* She stressed, however, that a booster vaccine does not "expand the profile" of immune responses against the component being vaccinated against. *Id.* at 247. Rather, it *decreases* the possibility of any bystander effects or antigenic mimicry presented by exposure to the wild virus at issue. *Id.* at 248. In her opinion, presensitization or an anamnestic response plays no role in the pathogenesis of an alleged vaccine-induced injury occurring in the innate system. *Id.* According to Dr. McCusker, the relevant scientific literature categorizes an anamnestic response as a cell-mediated product of the adaptive immune system (as opposed to a cytokine-mediated innate response). *Id.* at 250-52. And in any event, an adaptive response would require a delayed manifestation of symptoms (by at least seven to fourteen days following the inciting event). *Id.* at 250-51.

Apart from the above-identified deficiencies, Dr. McCusker also maintained that the scientific literature submitted could not reliably support any causal relationship between a vaccine and the development of TM *even if* one were to assume that an upregulation of IL-6 cytokines in the periphery somehow could cross the BBB under the present facts. Tr. at 284-85, 287. Dr. McCusker referenced Pidcock (submitted by Petitioners as supportive of a vaccine-induced TM injury), which she acknowledged indicated a *report* of a previous vaccination within 30 days of TM onset in 28 percent of the pediatric cases studied. *Id.* at 257; Pidcock at 1479. Upon review, however, Dr. McCusker noted that study actually concluded that there was no significant causal relationship between immunization and an onset of TM. Pidcock at 1479. Specifically, (as Dr. McCusker asserted at hearing) Pidcock's authors took into account the fact that young children receive many vaccines earlier in life (as recommended by the schedule), further weighing against any significant relationship. Tr. at 258-89; Pidcock at 1479.

Given Petitioners' reliance on the neutrophilic evidence in R.P.'s health record, Dr. McCusker next attempted to refute the argument that R.P.'s increased levels of neutrophils post-vaccination suggested a vaccine-related TM injury. Tr. at 301. Consistent with prior testimony, Dr. McCusker categorized neutrophils as the primary repair or defensive white blood cell in the innate system. *Id.* at 302.[40] She also acknowledged that neutrophils are the nonspecific, first

[40] In comparison, Dr. McCusker opined that lymphocytes (or secondary responders) are a part of the adaptive immune

responders to areas of inflammation and tissue damage in the body during an immune response. *Id.* In the context of the present matter, Dr. McCusker agreed that increased levels of neutrophils could indicate that R.P. was experiencing some underlying inflammation, but she contended that neutrophils cannot indicate *what* triggered their increased production or what caused the inflammation. *Id.* at 303.

Consistent with Dr. Lotze's testimony, Dr. McCusker asserted that R.P.'s TM (while idiopathic in nature) could more likely have been caused by his preexisting URI/otitis media than the subsequent vaccinations. Tr. at 244, 289.[41] At hearing, Dr. McCusker asserted that pediatric TM is commonly associated with an antecedent infection (with up to 71 percent of patients reporting some prior infection). *Id.* at 256-57; Second McCusker Rep. at 3. She acknowledged, on the other hand, that R.P.'s viral work-up (completed during his hospitalization) was negative, and that he appeared healthy at the time of vaccine administration. Tr. at 290. She opined, however, that a resolved infection could still be sufficiently pathogenic to result in the development of TM (via the typical, immune-mediated mechanisms such as antigenic mimicry or bystander activation). Second McCusker Rep. at 3. In her view, a resolution of symptoms (or even treatment of an infection with antibiotics, for example) did not change the initial "kick-up" of the immune response caused by that infection in the first place. Tr. at 259-60.

To support the above, Dr. McCusker pointed to an instance in the record where R.P.'s treating pediatrician diagnosed him with respiratory symptoms (and serous otitis media) during a visit in December 2012 (roughly three weeks prior to vaccine administration). *Id.* at 244. It was noted that R.P. was prescribed antibiotics as well. Ex. 8 at 31. During his hospital stay, an emergency room physician similarly opined that R.P.'s pre-vaccination respiratory symptoms could have played dome role in his development of TM. Second McCusker Rep. at 3; Ex. 8 at 31. Taken together, Dr. McCusker determined this prior infectious event was the more likely inciting event for R.P.'s TM. Tr. at 257; Second McCusker Rep. at 3.[42] Dr. McCusker otherwise could not identify any other test result supporting the conclusion that R.P.'s TM was related to any other

system that would appear later on in a disease process (i.e. in response to a specific harm or particular infection) and would be less numerous. Tr. at 301, 303.

[41] *See* T. Chonmaitree, et al., *Viral Upper Respiratory Tract Infection and Otitis Media Complication in Young Children*, 46 Clin. Infect. Diseases 815, 815 (2008), filed as Ex. E, Tab 1 (ECF No. 71-3) (finding more than 60 percent of URI episodes are accompanied by otitis media); M. Pettigrew, et al., *Viral-Bacterial Interactions and Risk of Acute Otitis Media Complicating Upper Respiratory Tract Infection*, 49 J. Clin. Microbiology 3750 (2011), filed as Ex. E, Tab 4 (ECF No. 71-6) (stating the same).

[42] Dr. McCusker also disputed some suggestions by Petitioners' experts that R.P.'s December 2011 symptoms were related to allergies or teething. Tr. at 261, 263. In her view, it would be uncommon for a six-month old child to be exposed to allergens sufficient to cause "allergic rhinitis" at such an early age. *Id.* at 261. With regard to teething, Dr. McCusker acknowledged that in the 1980s and 1990s, otitis media was considered to be associated with teething. *Id.* at 263. She opined, however, that more recent medical advancements have determined that ear/nose symptoms are not related to such a diagnosis, adding that Petitioners' experts relied on old literature in making this argument. *Id.* ("it's certainly not something that we teach medical students in 2018").

disease process (i.e. through an autoantibody or cell-mediated mechanism). Tr. at 277. She found the scientific literature to be supportive of this conclusion as well. *See* A. Borchers, et al., *Transverse Myelitis*, Autoimmun. Rev. 231, 238 (2012), filed as Ex. B, Tab 1 (ECF No. 70-4) ("TM in children is more frequently preceded by an infectious disease" as reported in 38 to 71 percent of cases); S. Beh, et al., *Transverse Myelitis*, 31 Neurol. Clin 79, 80 (2013), filed as Ex. B, Tab 2 (ECF No. 70-5) (half of patients presenting with TM have antecedent infection).

III. Procedural History

The Palattaos filed their petition on August 20, 2013. Pet. at 1. After gathering affidavits and various relevant medical records, Petitioners filed such materials and then their statement of completion on October 2, 2013 (though updated records were obtained and subsequently filed). ECF No. 10. Respondent thereafter filed his Rule 4(c) Report on December 2, 2013, indicating his view that Petitioners were not entitled to compensation because R.P.'s vaccinations could not be linked to onset of his TM based on the medical theory alleged. ECF No. 11.

Petitioners filed an initial expert report from Dr. Kinsbourne on January 6, 2014. ECF No. 12-1. An amended initial expert report was filed on April 21, 2014 (to correct a mistake by Dr. Kinsbourne). ECF No. 22-6. Respondent then filed his own expert reports in response on July 16, 2014 (including one from Dr. Lotze and one from Dr. McCusker). ECF No. 27. Following the filing of Respondent's reports, Petitioners filed an initial expert report from R.P.'s treating immunologist, Dr. Shapiro. ECF No. 39-1. Both parties filed supplemental expert reports thereafter. *See* ECF Nos. 40-1 (supplemental report from Dr. McCusker); 41-1 (supplemental report from Dr. Shapiro); 76-1 (supplemental report from Dr. Kinsbourne).

After the filing of these expert reports, the matter was originally set for hearing on February 23-24, 2017 in Minneapolis, Minnesota (ECF No. 45), but was subsequently rescheduled for May 17-18, 2018, in order to ensure that the case could be tried in Minnesota as desired by Petitioners. ECF No. 57. The parties filed pre-hearing submissions from February to April 2018, and the hearing went forward as scheduled. The parties elected to file post-hearing briefs, doing so by October 29, 2018. ECF Nos. 90-91. This matter is now ripe for adjudication.

IV. Applicable Legal Standards

A. *Petitioner's Overall Burden in Vaccine Program Cases*

To receive compensation in the Vaccine Program, a petitioner must prove either: (1) that she suffered a "Table Injury" – *i.e.*, an injury falling within the Vaccine Injury Table – corresponding to one of the vaccinations in question within a statutorily prescribed period of time

or, in the alternative, (2) that her illnesses were actually caused by a vaccine (a "Non-Table Injury"). *See* Sections 13(a)(1)(A), 11(c)(1), and 14(a), as amended by 42 C.F.R. § 100.3; § 11(c)(1)(C)(ii)(I); *see also Moberly v. Sec'y of Health & Human Servs*., 592 F.3d 1315, 1321 (Fed. Cir. 2010); *Capizzano v. Sec'y of Health & Human Servs*., 440 F.3d 1317, 1320 (Fed. Cir. 2006).[43] In this case, the Petitioners dismissed their Table claim.

For both Table and Non-Table claims, Vaccine Program petitioners bear a "preponderance of the evidence" burden of proof. Section 13(1)(a). That is, a petitioner must offer evidence that leads the "trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the judge of the fact's existence." *Moberly*, 592 F.3d at 1322 n.2; *see also Snowbank Enter. v. United States*, 6 Cl. Ct. 476, 486 (1984) (mere conjecture or speculation is insufficient under a preponderance standard). Proof of medical certainty is not required. *Bunting v. Sec'y of Health & Human Servs*., 931 F.2d 867, 873 (Fed. Cir. 1991). In particular, a petitioner must demonstrate that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly*, 592 F.3d at 1321 (quoting *Shyface v. Sec'y of Health & Human Servs*., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); *Pafford v. Sec'y of Health & Human Servs*., 451 F.3d 1352, 1355 (Fed. Cir. 2006). A petitioner may not receive a Vaccine Program award based solely on her assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. Section 13(a)(1).

In attempting to establish entitlement to a Vaccine Program award of compensation for a Non-Table claim, a petitioner must satisfy all three of the elements established by the Federal Circuit in *Althen v. Secretary of Health & Human Services*: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Althen*, 418 F.3d 1274, 1278 (Fed. Cir. 2005).

Each of the *Althen* prongs requires a different showing. Under *Althen* prong one, petitioners must provide a "reputable medical theory," demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford*, 451 F.3d at 1355-56 (citations omitted). To satisfy this prong, a petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). Such a theory must only be "legally probable, not medically or scientifically certain." *Id*. at 549.

[43] Decisions of special masters (some of which I reference in this ruling) constitute persuasive but not binding authority. *Hanlon v. Sec'y of Health & Human Servs.*, 40 Fed. Cl. 625, 630 (1998). By contrast, Federal Circuit rulings concerning legal issues are binding on special masters. *Guillory v. Sec'y of Health & Human Servs.*, 59 Fed. Cl. 121, 124 (2003), *aff'd*, 104 F. App'x 712 (Fed. Cir. 2004); *see also Spooner v. Sec'y of Health & Human Servs.*, No. 13-159V, 2014 WL 504728, at *7 n.12 (Fed. Cl. Spec. Mstr. Jan. 16, 2014).

Petitioners may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1378-79 (Fed. Cir. 2009) (citing *Capizzano*, 440 F.3d at 1325-26). Special masters, despite their expertise, are not empowered by statute to conclusively resolve what are essentially thorny scientific and medical questions, and thus scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Id.* at 1380. Accordingly, special masters must take care not to increase the burden placed on petitioners in offering a scientific theory linking vaccine to injury. *Contreras v. Sec'y of Health & Human Servs.*, 121 Fed. Cl. 230, 245 (2015) ("[p]lausibility . . . in many cases *may* be enough to satisfy *Althen* prong one" (emphasis in original)), *vacated on other grounds*, 844 F.3d 1363 (Fed. Cir. 2017); *see also Andreu*, 569 F.3d at 1375. But this does not negate or reduce a petitioner's ultimate burden to establish her overall entitlement to damages by preponderant evidence. *W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1356 (Fed. Cir. 2013) (citations omitted).[44]

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). In establishing that a vaccine "did cause" injury, the opinions and views of the injured party's treating physicians are entitled to some weight. *Andreu*, 569 F.3d at 1367; *Capizzano*, 440 F.3d at 1326 ("medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury'") (quoting *Althen*, 418 F.3d at 1280). Medical records are generally viewed as particularly trustworthy evidence, since they are created contemporaneously with the treatment of the patient. *Cucuras v. Sec'y of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993).

However, medical records and/or statements of a treating physician's views do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. Section 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 746 n.67 (2009) ("there is nothing . . . that mandates that the testimony of a treating physician is sacrosanct – that it must be

[44] There is ample contrary authority for the more straightforward proposition that the first *Althen* prong, like the overall test itself, simply applies a preponderance standard when evaluating if a reliable and plausible causal theory has been established. *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1350 (Fed. Cir. 2010). For purposes of the present analysis, I am stressing those cases focusing on the *plausibility* of the causal theory proposed, as opposed to whether preponderant evidence supports it, in order to avoid imposing on Petitioners a greater evidentiary burden than the law requires. This does not, however, change the fact that *any* theory's plausibility, for purposes of satisfying the *Althen* test, is properly analyzed by subjecting its components to the *Daubert* tests for scientific reliability. *Terran v. Sec'y of Health & Human Servs*., 195 F.3d 1302, 1316 (Fed. Cir. 1999).

accepted in its entirety and cannot be rebutted"). As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should also be weighed against other, contrary evidence also present in the record – including conflicting opinions among such individuals. *Hibbard v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 742, 749 (2011) (not arbitrary or capricious for special master to weigh competing treating physicians' conclusions against each other), *aff'd*, 698 F.3d 1355 (Fed. Cir. 2012); *Caves v. Sec'y of Dep't of Health & Human Servs.*, 100 Fed. Cl. 119, 136 (2011), *aff'd*, 463 F. App'x 932 (Fed. Cir. 2012); *Veryzer v. Sec'y of Health & Human Servs.*, No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), *mot. for review den'd*, 100 Fed. Cl. 344, 356 (2011), *aff'd without opinion*, 475 Fed. App'x 765 (Fed. Cir. 2012).

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id*. at 1352; *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 2013 WL 1896173 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Human Servs.*, No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

B. *Law Governing Analysis of Fact Evidence*

The process for making determinations in Vaccine Program cases regarding factual issues begins with consideration of the medical records. Section 11(c)(2). The special master is required to consider "all [] relevant medical and scientific evidence contained in the record," including "any diagnosis, conclusion, medical judgment, or autopsy or coroner's report which is contained in the record regarding the nature, causation, and aggravation of the petitioner's illness, disability, injury, condition, or death," as well as "the results of any diagnostic or evaluative test which are contained in the record and the summaries and conclusions." Section 13(b)(1)(A). The special master is then required to weigh the evidence presented, including contemporaneous medical records and testimony. *See Burns v. Sec'y of Health & Human Servs*., 3 F.3d 415, 417 (Fed. Cir. 1993) (it is within the special master's discretion to determine whether to afford greater weight to contemporaneous medical records than to other evidence, such as oral testimony surrounding the events in question that was given at a later date, provided that such a determination is evidenced by a rational determination).

Medical records that are created contemporaneously with the events they describe are presumed to be accurate and "complete" (*i.e.*, presenting all relevant information on a patient's health problems). *Cucuras*, 993 F.2d at 1528; *Doe/70 v. Sec'y of Health & Human Servs.*, 95 Fed. Cl. 598, 608 (2010) ("[g]iven the inconsistencies between petitioner's testimony and his contemporaneous medical records, the special master's decision to rely on petitioner's medical records was rational and consistent with applicable law"), *aff'd*, *Rickett v. Sec'y of Health & Human Servs.*, 468 F. App'x 952 (Fed. Cir. 2011) (non-precedential opinion). This presumption is based on the linked propositions that (i) sick people visit medical professionals; (ii) sick people honestly report their health problems to those professionals; and (iii) medical professionals record what they are told or observe when examining their patients in as accurate a manner as possible, so that they are aware of enough relevant facts to make appropriate treatment decisions. *Sanchez v. Sec'y of Health & Human Servs*., No. 11-685V, 2013 WL 1880825, at *2 (Fed. Cl. Spec. Mstr. Apr. 10, 2013); *Cucuras v. Sec'y of Health & Human Servs*., 26 Cl. Ct. 537, 543 (1992), *aff'd*, 993 F.2d 1525 (Fed. Cir. 1993) ("[i]t strains reason to conclude that petitioners would fail to accurately report the onset of their daughter's symptoms. It is equally unlikely that pediatric neurologists, who are trained in taking medical histories concerning the onset of neurologically significant symptoms, would consistently but erroneously report the onset of seizures a week after they in fact occurred").

Accordingly, if the medical records are clear, consistent, and complete, then they should be afforded substantial weight. *Lowrie v. Sec'y of Health & Human Servs*., No. 03-1585V, 2005 WL 6117475, at *20 (Fed. Cl. Spec. Mstr. Dec. 12, 2005). Indeed, contemporaneously medical records are generally found to be deserving of greater evidentiary weight than oral testimony – especially where such testimony conflicts with the record evidence. *Cucuras*, 993 F.2d at 1528; *see also Murphy v. Sec'y of Health & Human Servs.*, 23 Cl. Ct. 726, 733 (1991), *aff'd*, 968 F.2d 1226 (Fed. Cir.), *cert. den'd*, *Murphy v. Sullivan*, 506 U.S. 974 (1992) (citing *United States v. United States Gypsum Co.*, 333 U.S. 364, 396 (1947) ("[i]t has generally been held that oral testimony which is in conflict with contemporaneous documents is entitled to little evidentiary weight.")).

However, there are situations in which compelling oral testimony may be more persuasive than written records, such as where records are deemed to be incomplete or inaccurate. *Campbell v. Sec'y of Health & Human Servs*., 69 Fed. Cl. 775, 779 (2006) ("like any norm based upon common sense and experience, this rule should not be treated as an absolute and must yield where the factual predicates for its application are weak or lacking"); *Lowrie*, 2005 WL 6117475, at *19 ("[w]ritten records which are, themselves, inconsistent, should be accorded less deference than those which are internally consistent") (quoting *Murphy v. Sec'y of Health & Human Servs.*, 23 Cl. Ct. 726, 733 (1991), *aff'd per curiam*, 968 F.2d 1226 (Fed. Cir. 1992)). Ultimately, a determination regarding a witness's credibility is needed when determining the weight that such

testimony should be afforded. *Andreu*, 569 F.3d at 1379; *Bradley v. Sec'y of Health & Human Servs.*, 991 F.2d 1570, 1575 (Fed. Cir. 1993).

C. *Analysis of Expert Testimony*

Establishing a sound and reliable medical theory often requires a petitioner to present expert testimony in support of his claim. *Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1361 (Fed. Cir. 2000). Vaccine Program expert testimony is usually evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594-96 (1993). *See Cedillo v. Sec'y of Health & Human Servs.*, 617 F.3d 1328, 1339 (Fed. Cir. 2010) (citing *Terran v. Sec'y of Health & Human Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999)). "The *Daubert* factors for analyzing the reliability of testimony are: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community." *Terran*, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592-95).

The *Daubert* factors play a slightly different role in Vaccine Program cases than they do when applied in other federal judicial fora (such as the district courts). *Daubert* factors are usually employed by judges (in the performance of their evidentiary gatekeeper roles) to exclude evidence that is unreliable and/or could confuse a jury. In Vaccine Program cases, by contrast, these factors are used in the *weighing* of the reliability of scientific evidence proffered. *Davis v. Sec'y of Health & Human Servs.*, 94 Fed. Cl. 53, 66-67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"). The flexible use of the *Daubert* factors to evaluate the persuasiveness and reliability of expert testimony has routinely been upheld. *See, e.g.*, *Snyder*, 88 Fed. Cl. at 742-45. In this matter (as in numerous other Vaccine Program cases), *Daubert* has not been employed at the threshold, to determine what evidence should be admitted, but instead to determine whether expert testimony offered is reliable and/or persuasive.

Respondent frequently offers one or more experts of her own in order to rebut a petitioner's case. Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d at 1362). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 146 (1997)); *see also Isaac v. Sec'y of Health & Human Servs.*, No. 08-601V, 2012 WL 3609993, at *17 (Fed. Cl. Spec. Mstr. July 30, 2012), *mot. for*

review den'd, 108 Fed. Cl. 743 (2013), *aff'd*, 540 Fed. App'x 999 (Fed. Cir. 2013) (citing *Cedillo*, 617 F.3d at 1339).

Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Moberly*, 592 F.3d at 1325-26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Human Servs*., 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act"). It is in the exercise of my duties as a special master to weigh competing expert testimony. *Copenhaver v. Sec'y of Health & Human Servs.*, No. 13-1002V, 2016 WL 6947389, at *5 (Fed. Cl. Oct. 20, 2016) ("Special Masters may use their discretion in weighing expert testimony, and case law supports that discretion").

In determining whether a particular expert's testimony was reliable or credible, I may consider whether the expert offers an opinion that exceeds his training or competence. *Walton v. Sec'y of Health & Human Servs.*, No. 04-503V, 2007 WL 1467307, at *17-18 (Fed. Cl. Spec. Mstr. Apr. 30, 2007) (otolaryngologist not well suited to testify about disciplines other than her own specialty). While (in keeping with the liberality with which evidence offered in Vaccine Program cases is treated) I heard and have considered all of the testimony of the experts offered at the entitlement hearing, I may properly evaluate, and give appropriate weight to, whether certain testimony is beyond a particular expert's purview. *See, e.g., King v. Sec'y of Health & Human Servs.*, No. 03-584V, 2010 WL 892296, at *78-79 (Fed. Cl. Spec. Mstr. Mar. 12, 2010) (petitioner's expert far less qualified to offer opinion on general causation issues pertaining to autism than specific issues pertaining to the petitioner's actual medical history, given the nature of the expert's qualifications).

D. *Consideration of Medical Literature*

Both parties filed medical and scientific literature in this case, including some articles (such as those discussing molecular mimicry and protein sequences in vaccines) that do not factor into the outcome of this decision. I have reviewed all of the medical literature submitted in this case, but I only discuss those articles that are most relevant to my determination and/or are central to Petitioners' case – just as I have not exhaustively discussed every individual medical record filed. *Moriarty v. Sec'y of Health & Human Servs.*, 844 F.3d 1322, 1328 (Fed. Cir. 2016) ("[w]e generally presume that a special master considered the relevant record evidence even though he does not explicitly reference such evidence in his decision") (citation omitted); *see also Paterek v. v. Sec'y of Health & Human Servs.,* 527 F. App'x 875, 884 (Fed. Cir. 2013) ("[f]inding certain

information not relevant does not lead to — and likely undermines — the conclusion that it was not considered").

ANALYSIS

I address the three *Althen* prongs in order of their relevance to my determination, rather than in the sequential order set forth by the Federal Circuit.

I. *Althen* Prong Three

Because of the close relationship between the first and third *Althen* prongs, petitioners are obligated to establish that the timing of onset of symptoms is "medically appropriate" under their proposed causation theory. *See, e.g., de Bazan*, 539 F.3d at 1352 (the explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement)); *Shapiro*, 101 Fed. Cl. at 542.

As discussed below, although I am also cognizant of the fact that other claimants have succeeded in establishing that a vaccine could cause TM, there are problems with the particular causation theory offered herein. But even assuming that the "can cause" element had been satisfied, Petitioners' theory would still founder on the very short timeframe in which his TM developed.

A. *R.P.'s TM Most Likely Had an Onset of January 8, 2013*

A threshold issue to resolve is when R.P.'s TM more likely than not began. Petitioners' experts were somewhat inconsistent in pinpointing an onset time, but their overall position seems to be that although R.P. experienced some immediate post-vaccination malaise-like symptoms on January 7, 2013, his actual neurologic symptoms that heralded the start of his subsequently-diagnosed TM only manifested on January 9th, after the Palattaos took him a second time to the ER.

However, the record better supports the conclusion that R.P.'s initial manifestations of TM began during the day of January 8, 2013. Besides running a fever that day (and the contemporaneous ER records strongly suggest that his fevers did not simply began after R.P. was picked up from day care, but occurred throughout that day, and may have even been evident that morning), the very reason R.P. was taken to the ER that evening was due to Petitioners' alarm at his condition – and specifically after contacting R.P.'s pediatrician. Ex. 8 at 39-40. The symptoms that prompted that visit were not mere post-vaccination malaise, but concerns about R.P.'s breathing and inability to sit up or move. *Id.* at 40. In addition, there appears to have been reasoned worries about his urinary output – a notation that Dr. Lotze, the sole pediatric neurologist who testified in this case, and the medical expert with the most demonstrated direct expertise with pediatric TM, deemed significant. Tr. at 187-88, 200.

Petitioners argue in response that the fact that R.P.'s neurologic evaluation that evening did not fully confirm that anything was (then) wrong somehow eliminates the significance of the presentation that led them to take R.P. to the ER that night in the first place. But there are two deficiencies in that argument. First, as Dr. Lotze pointed out, it does not appear that this evaluation was conducted by a neurologist, suggesting it might have been incomplete. Tr. at 187, 210. Second, and more important, the fact that presenting symptoms might not immediately be understood to be the harbinger of a particular illness does not, under well-accepted Program case law, mean that onset did not occur sooner than treaters immediately recognized. *See, e.g.*, *Goetz v. Sec'y of Health & Human Servs.*, 45 Fed. Cl. 340, 342 (1999) (stating that it is "the occurrence of an event recognizable as a sign of [an injury] by the medical profession at large, not the diagnosis that actually confirms such an injury in a specific case."), *aff'd*, 4 F. App'x 827 (Fed. Cir. 2001).

The Vaccine Program measures onset from the first manifestation of a symptom – *regardless of whether it is recognized as such*. *See, e.g., Markovich v. Sec'y of Health & Human Servs.*, 477 F.3d 1353 (Fed. Cir. 2007); *Gramza v. Sec'y of Health & Human Servs.*, No. 15-247V, 2018 WL 1581674, at *15 (Fed. Cl. Spec. Mstr. Feb. 5, 2018) (citing 42 U.S.C. § 300aa–16(a)(2)), *mot. for review den'd*, 139 Fed. Cl. 309 (2018). As a result, the fact that R.P.'s January 8th symptoms did not immediately lead to a TM diagnosis (and indeed, were deemed at that time mild enough to permit him to go home that evening) does not diminish their significance when the greater record is considered – especially in light of the fact that he was taken back to the ER the next morning.

B. *Onset of R.P.'s TM Began Too Soon After Vaccination to be Deemed Medically Reasonable*

Under the causation theory proposed by Dr. Kinsbourne, R.P.'s innate immune system, in reaction to the vaccinations he received the morning of January 7, 2013, overproduced cytokines (in particular, IL-6) in sufficient amounts, and in a short period of time, to cause them to breach the BBB and initiate a demyelinating attack on his spinal cord. Based upon my onset determination, this attack began to manifest symptoms the following afternoon – meaning the process advanced from vaccination to harm within 30 to 36 hours.

This proposed timeframe is not medically reasonable – and its insufficiency can be demonstrated based on the very literature filed by Petitioners to support their theory. As explained by Dr. McCusker, the best evidence in support of Petitioners' theory is Kaplin I – but under it, the onset of a spinal cord demyelinating injury attributable to excess cytokine production could not reasonably begin before the passage of *several days* post-vaccination. Tr. at 251-52, 288. And Kaplin I featured the direct introduction of large amounts of cytokines into animal spinal cords – not the migration from the periphery of cytokines produced in natural response to vaccines. Thirty-six hours is simply too short a period for such a process to occur and still be medically reasonable.[45]

[45] In addition, even if a somewhat short timeframe – say 48 to 72 hours – *had* been established as medically acceptable,

Besides the above, Petitioners relied on numerous case reports (or review articles discussing case reports) to bulwark their timeframe arguments. But case reports are well understood in the Program to be weak evidence (although they have some value nonetheless). *See, e.g., Campbell v. Sec'y of Health & Human Servs.*, 97 Fed. Cl. 650, 668 (2011) ("[c]ase reports do not purport to establish causation definitively, and this deficiency does indeed reduce their evidentiary value . . . [but] the fact that case reports can by their nature only present indicia of causation does not deprive them of all evidentiary weight."). Moreover, the case reports offered herein involving pediatric cases of TM largely display timeframes *exceeding* what R.P. experienced. *See, e.g.,* Agmon-Levin at 1200 (three case reports of months-old children who developed TM between six and seventeen days post-vaccination); Whittle at 1450 (six to seven days post-vaccination onset); Riel-Romero at 688 (seventeen days). By contrast, those case reports with shorter timeframes (for example, the two-hour onset in Savas) involved symptoms that did not become fulminant for months – again, not comparable to what R.P. experienced.

The arguments of Petitioners' experts that another possible causation mechanism – the sensitization of the innate immune system, attributable to prior doses of certain vaccines (in Dr. Kinsbourne's view, most likely those containing tetanus) received earlier in a child's life[46] – could explain the rapid onset of TM post-vaccination were also unreliably supported. The main item of literature offered to substantiate this concept (which relied on a mechanism that neither of Petitioners' experts discussed at hearing as much as the broader argument about the pathologic results of overproduction of cytokines) was Netea. But that article itself does not suggest that innate system memory, if prompted by a vaccine, could have a pathologic outcome, and Dr. McCusker pointed out that vaccination generally was more likely to encourage *adaptive* system memory. Tr. at 247-48. Moreover, Petitioners offered no additional literature taking the issue one step further – for example, literature exploring the pathologic potential of the concepts proposed in Netea. Netea's addressing of the topic in the context of the innate system thus raised interesting possibilities for future study – but does not stand by itself as a strong piece of evidence explaining the rapid onset of R.P.'s TM, especially in light of the core components of Petitioners' causation theory.

Finally, I take note of the decisions of other special masters when considering reasonable onset timeframes for vaccine-caused TM in infants. While such decisions have allowed for the plausibility that TM could be vaccine-caused, they have dismissed cases involving onsets too close

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Dr. McCusker persuasively argued that the 30 to 36-hour period from the January 7, 2013 vaccinations to onset the following afternoon means that whatever triggered R.P.'s TM likely occurred *before* he received the vaccines in question. Second McCusker Rep. at 3; *see* Tr. at 244, 257.

[46] Arguably, this was Dr. Shapiro's initial causation theory at the time he first saw R.P. in 2013. *See* Ex. 6 at 8. However, at hearing, Dr. Shapiro seemed to rely on this somewhat less. *See* Tr. at 128. Through his testimony, Dr. Kinsbourne posited that Netea supports his conclusion that the innate immune system can be amplified (or "sensitized") upon reexposure to an invading antigen. Tr. at 353-54. As noted earlier, however, Dr. Kinsbourne does not persuasively explain how this reexposure (and resulting "amplification") of the innate system could result in (or hasten) a pathologic process resulting in TM. *See id.* at 354.

in time to the vaccination to be medically reasonable. *See, e.g.*, *Mosley v. Sec'y of Health & Human Servs.*, No. 08-724V, 2015 WL 2354316, at *19 (Fed. Cl. Spec. Mstr. Apr. 27, 2015) ("onset of TM one day after tetanus vaccine is too soon to support vaccine causation"); *Jagoe v. Sec'y of Health & Human Servs.*, No. 08-678V, 2012 WL 13036265, at *28 (Fed. Cl. Spec. Mstr. Aug. 3, 2012) (twenty-four-hour onset is not medically appropriate for a vaccine-induced TM injury); *Crosby v. Sec'y of Health & Human Servs*., No. 08-799V, 2012 WL 13036266, at *38-39 (Fed. Cl. Spec. Mstr. June 20, 2012) (finding the same). Here, although the 30 to 36-hour period is slightly longer, I find it also is too soon to be medically acceptable, and therefore the failure to establish the third *Althen* prong is fatal to Petitioners' claim.

II. ***Althen* Prong One**

The concept that a vaccine could cause a demyelinating condition is consistent with other successful causation theories frequently proposed in Program cases. *See, e.g.*, *Schmidt v. Sec'y of Health & Human Servs.*, No. 07-20V, 2009 WL 5196169 (Fed. Cl. Spec. Mstr. Dec. 17, 2009). Other special masters have also ruled that a variety of vaccines can initiate an autoimmune process resulting in TM. *Raymo v. Sec'y of Health & Human Servs.*, No. 11-0654V, 2014 WL 1092274, at *1 (Fed. Cl. Spec. Mstr. Feb. 24, 2014). And petitioners have succeeded in obtaining entitlement awards based upon such injuries incurred by infants. *See, e.g.*, *Bowes v. Sec'y of Health & Human Servs.*, No. 01-481V, 2006 WL 2849816 (Fed. Cl. Spec. Mstr. Sept. 8, 2006) (two-week onset of TM post vaccination in four-month-old infant found to be causal). While these decisions do not bind me, I take note of them and their sound analyses.

In the present matter, however, Petitioners' experts conceded at the outset that the mechanism most frequently offered by Program petitioners to explain how a vaccine might precipitate a demyelinating illness like TM via an autoimmune process – molecular mimicry (involving an adaptive immune response resulting in autoimmune disease) – is inapplicable in this case. Petitioners also do not claim that any specific component of the vaccines R.P. received are integral to their theory. Of course, Program petitioners are not required to offer direct proof supporting their theory, or even any specific type of evidence, but instead may rely on circumstantial evidence. *See, e.g., Althen,* 418 F.3d at 1280. Regardless of *what* kind of evidence is relied upon, however, claimants must still establish preponderant proof. And in addressing the first *Althen* prong, that proof must go toward establishing a reliable scientific or medical theory – and if it comes in the form of a scientific or medical article, it must be reliable. *Knudsen*, 35 F.3d at 548.

Petitioners argued that the immunologic stimulation that vaccinations generally provide (which inherently encourage cytokine production) could result in a demyelinating condition like TM. Petitioners' theory was rooted in the general proposition that virtually *any* vaccine could be pathogenic and result in TM. *See* Tr. at 160. But they have offered insufficient reliable scientific or medical evidence that addresses the specific pathogenicity of the vaccines in dispute herein, nor

anything connecting vaccines to TM based merely on their recognized pro-inflammatory capacities. And the literature they rely upon does not reliably establish that cytokines *can* instigate a process resulting in TM.

A few overarching aspects of this theory are medically or scientifically sound. Petitioners offered persuasive evidence in support of their contention that IL-6 cytokine levels are elevated in patients diagnosed with TM. Kaplin I at 2733, 2738; Kaplin II at 5; Graber at 124. In addition, they have submitted relevant and reliable animal model studies (in particular, those referenced in Kaplin I) supporting the contention that IL-6 (when injected directly into the spinal cord in high amounts) is implicated in the disease process resulting in TM. Kaplin I at 2735.

Where Petitioners' theory falters, however, is in its specifics, for many of its most important elements are inadequately supported. In particular, Petitioners have failed to demonstrate that cytokine upregulation in the periphery attributable to a vaccine can *also* trigger TM. Much of the literature that Petitioners rely upon, like Kashiwagi, mostly discusses the expected manner in which vaccines cause cytokine upregulation – *not* the possible pathogenic results of that same vaccine-induced upregulation. *See, e.g.*, Kashiwagi. Kashiwagi in particular is not especially persuasive evidence for this critical part of the causation theory (even though it may stand as reliable science about the promotion of cytokines after vaccination). As I observed in a different decision, "Kashiwagi does not support the idea that cytokines produced in response to vaccination could negatively impact the brain in the way [Petitioners' expert] proposes herein." *Dean v. Sec'y of Health & Human Servs.,* No. 13-808V, 2017 WL 2926605, at *17 (Fed. Cl. Spec. Mstr. June 9, 2017), *citing Copenhaver v. Sec'y of Health & Human Servs*., No. 13-1002V, 2016 WL 3456436, at *9-14 (Fed. Cl. Spec. Mstr. May 31, 2016) (infant's death not caused by cytokine upregulation due to vaccination), *mot. for review den'd*, 129 Fed. Cl. 176 (2016); *Cozart v. Sec'y of Health & Human Servs*., No. 00-590V, 2015 WL 6746499, at *6-7 (Fed. Cl. Spec. Mstr. Oct. 15, 2015), *mot. for review den'd*, 126 Fed. Cl. 488 (2016).

The concept that vaccination can promote production of cytokines that have an inflammatory capacity is often pointed to by claimants in attempting to explain a vaccine's causal role in their illness. But claimants cannot transmute scientific evidence exploring how vaccines normally function in the immune system into a reliable and persuasive causation theory that *any* vaccine can be pathogenic without a more specific showing that applies to the circumstances at hand. *Olson v. Sec'y of Health & Human Servs.,* No. 13-439V, 2017 WL 3624085 (Fed. Cl. Spec. Mstr. July 14, 2017), *mot. for review den'd*, 135 Fed. Cl. 670 (2017), *aff'd*, 2018 WL 6721291 (Fed. Cir. Dec. 21, 2018). It is too far a leap from the valid science establishing what cytokines do generally, or the role they play in encouraging TM (once it has already been initiated by infection or some other trigger), to conclude they are also likely causal of it. *Copenhaver*, 2016 WL 3456436, at *13-15, 17.

Beyond the above, Petitioners relied on review articles discussing case studies, which do not themselves stand as robust evidence of causation, or articles that simply observe an association between the diagnosis of TM and a studied individual having received a vaccination in the time before onset. *See, e.g.*, Agmon-Levin; Pickcock; Kerr. And many of the existing Program decisions in which TM has been found to be caused by a vaccine rely on a mechanism (molecular mimicry between vaccine antigen and self-proteins resulting in autoimmune cross-reaction) that Petitioners' experts herein disavowed as relevant. *See, e.g.*, *Roberts v. Sec'y of Health & Human Servs.*, No. 09-427V, 2013 WL 5314698 (Fed. Cl. Spec. Mstr. Aug. 29, 2013); *Hargrove v. Sec'y of Health & Human Servs.*, No. 05-0694V, 2009 WL 1220986 (Fed. Cl. Spec. Mstr. Apr. 14, 2009); Tr. at 105.

The epidemiologic evidence offered in this case also undercuts Petitioners' argument. I give *some* weight to the Baxter epidemiologic study, which suggests no association between the relevant vaccines in this case and TM. Although it is unquestionably the case that Vaccine Program litigants need not offer epidemiologic evidence to prevail, special masters may take note of its existence and consider it when determining if a claimant has met his burden of proof. *See, e.g.*, *D'Toile v. Sec'y of Health & Human Servs.*, 726 F. App'x 809, 811-12 (Fed. Cir. 2018); *Taylor v. Sec'y of Health & Human Servs.*, 108 Fed. Cl. 807, 819-21 (Fed. Cl. 2013) (special master did not err in considering epidemiological evidence); *Andreu*, 569 F.3d at 1379 (a special master may assess epidemiological evidence in "reaching an informed judgment as to whether a particular vaccination likely caused a particular injury").

Finally, Petitioners' experts were unpersuasive in imbuing any of their theories with heft that the filed literature could not provide. Dr. Kinsbourne for the most part explained his theory clearly, but lacked the personal expertise (whether from research into the innate immune system, or the recent treatment of TM) that could have given Petitioners' causation theory the ballast lacking in the filed literature he curated for this case. Dr. Shapiro has comparatively more expertise with immunologic treatment, but he too could not speak to research or specialized knowledge that could breathe additional life into the proposed causation theory.

All told, Petitioners' theory of causation was unpersuasive and unreliable. It depended too much on the expected manner in which vaccines work to become pathologic, without offering reliable scientific evidence to substantiate the plausibility of the latter, and the theory as presented (which depends on error by the innate immune system) was not consistent with other versions that have been successfully established in other Program cases.

III. ***Althen* Prong Two**

The aforementioned deficiencies in Petitioners' causation theory, plus the lack of preponderant evidence establishing that the timeframe for onset of R.P.'s post-vaccination TM was medically reasonable, make it unnecessary to perform a full evaluation on their success at establishing the "did cause" second prong of the *Althen* test. *See, e.g., Bigbee v. Sec'y of Health &*

Human Servs., No. 06-663V, 2012 WL 1237759, at *36 (Fed. Cl. Spec. Mstr. Mar. 22, 2012) (citing *Broekelschen v. Sec'y of Health & Human Servs.*, 89 Fed. Cl. 336, 346 (2009)). However, I will briefly review Petitioners' showing on this prong as well.

Petitioners were unable to point to any test results or other clinical evidence that suggested the causal process their experts proposed actually occurred in R.P.'s case as theorized. Indeed, Dr. Shapiro seems to have recognized this at the time of his first visit with R.P. in the summer of 2013 (although, as discussed below, he maintained then, and still does, that the absence of evidence of a viral cause or other explanation for R.P.'s TM is significant). Tr. at 132, 153-54, 175, 318; First Shapiro Rep. at 3. Treater support for Petitioners' theory is also inconclusive. Dr. Pozos and treaters at Gillette discounted any role for the vaccinations in R.P.'s disease course – pointing instead to an unspecified viral etiology (which Dr. Pozos attributed to R.P.'s December 2012 URI). Ex. 4 at 9, Ex. 5 at 23. However, Nurse Practitioner Epland and her colleague, Dr. Shapiro, both identified the vaccinations as likely causal, and neurologist Dr. Janousek later echoed their views (although it seems reasonable to infer that his diagnosis was influenced by the Midwest Immunology Clinic professionals, to whom Dr. Janousek first referred R.P.). Ex. 9 at 23.

Dr. Shapiro specifically invoked the presence of excessive neutrophils in R.P.'s CSF from his initial testing performed on R.P. around the time of his hospitalization in mid-January 2013 as confirming his theory – because those neutrophils presumably establish an uncontrolled innate immune response. But Petitioners did not successfully establish the predicate for this argument: that excess neutrophils *are first-order evidence of TM* that has been brought on by an overactive innate immune system response mediated by cytokines (as opposed to TM mediated by an autoimmune cross-reaction attributable to molecular mimicry). At best, all experts who discussed the subject at hearing agreed that neutrophils were evidence only of an immediate innate immune response (and therefore *secondary* proof of some inflammation in the body – here, in the central nervous system) - and Respondent's experts persuasively argued that the neutrophil-predominant CSF readings were evidence of nothing more than that. In contrast, nothing that Dr. Shapiro argued or offered (in particular, Matas) established that a CSF reading high in neutrophils was either (a) specific to TM brought about by the proposed innate mechanism, or (b) evidence that the pathogenic process resulting in TM was an innate immune system process. Dr. Shapiro merely seemed to be of the opinion that because his theory assumed a disease process mediated by the innate immune system, any evidence of the innate immune system working in R.P.'s case proved the theory.

Petitioners and their experts otherwise put great stock in the argument that no other plausible explanation for the etiology of R.P.'s TM existed, allowing for the conclusion that the vaccines he received must be causal. *See, e.g.*, Tr. at 143 ("the lack of other factors . . . could explain it"), 149 ("it's very clear in my mind that there is no other good explanation"), 310 ("we have no other factor with evidence that we can invoke that could explain it"); *see also* Ex. 6 at 8. But there are several overlapping logical and legal errors in such reasoning. First, Program law does *not* stand for the proposition that petitioners demonstrate entitlement by showing that

alternative causes known to be associated with a condition are absent or unsupported by the record. *See, e.g.*, *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1149-50 (Fed. Cir. 1992) ("evidence showing an absence of other causes does not meet petitioner's affirmative duty to show actual or legal causation"). Indeed, the burden of proof does not shift to Respondent to prove an alternative cause *until* a petitioner carries his initial burden of proof. *See, e.g.*, *Rus v. Sec'y of Health & Human Servs.*, 129 Fed. Cl. 672, 680 (2016) ("if a petitioner establishes a *prima facie* case, the burden shifts to the respondent to show, by a preponderance of the evidence, that the injury was caused by a factor unrelated to the vaccine"). At all times, the petitioner must show preponderantly that the relevant vaccine(s) *did* likely cause his injury – not that other things could *not* have done so.[47]

Second, the evidence regarding explanations for the cause of R.P.'s TM is far more ambiguous than Petitioners allow. The record establishes that R.P. likely had some kind of URI in December 2012 (as evidenced by contemporaneous statements to treaters at that time that R.P. had been experiencing URI-like symptoms for more than a week), even if it is also the case that the Palattaos brought R.P. to the pediatrician in part out of a reasonable concern that he might have an ear infection (and obtained antibiotics to treat it prophylactically over the 2012 Christmas holiday). Certainly treaters who thereafter saw R.P. close in time to his hospitalization found that diagnosis significant. *See, e.g.*, Ex. 5 at 24, 37; Ex. 4 at 9. And Respondent's experts both observed (based on reliable literature as well as their own expertise with TM) that in the majority of pediatric TM cases, a virus or URI preceded onset of neurologic symptoms. Tr. at 192, 256-57.

Petitioners reasonably respond by pointing to the lack of record evidence *identifying* the virus in question, as reflected by testing performed at the time of R.P.'s initial hospitalization that could not specify an existing infectious process, whether viral or bacterial. But the inability to determine in the course of this proceeding the actual cause of R.P.'s tragic injury does not aid Petitioners. For, as Respondents' experts noted, TM is often deemed idiopathic. And in any event, even if Respondent could not on the basis of the present record establish preponderant evidence of an alternative cause of R.P.'s TM, the burden never shifted to Respondent to do so in the first place. *See, e.g.*, *Rus*, 129 Fed. Cl. at 680.

CONCLUSION

R.P. and his family have unquestionably suffered greatly as result of the illness he experienced (and continues to struggle with), and Petitioners articulately testified to the challenges they face in dealing with it. Their claim reflects a good faith effort to establish a causal theory

[47] A corollary point is that petitioners cannot prove causation simply on the basis of a temporal association between the vaccine at the relevant injury. *See, e.g.*, *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1149-50 (Fed. Cir. 1992) ("evidence showing absence of other causes does not meet petitioner's affirmative duty to show actual or legal causation").

based on what appeared a potential explanation for his TM, and it had many elements of evidentiary support. But my personal sympathies for Petitioners' effort in adjudicating this claim are not a basis for an entitlement decision. Rather, such a decision must be the product of a careful review of the evidence, balanced in light of the applicable legal standards based upon probative weight and overall persuasiveness. Here, that balancing leads me to conclude that the Palattaos were unable to carry their burden of proof, and therefore I must DENY entitlement in this case.

In the absence of a timely-filed motion for review (see Appendix B to the Rules of the Court), the Clerk shall enter judgment in accord with this decision.[48]

IT IS SO ORDERED.

/s/ Brian H. Corcoran
Brian H. Corcoran
Special Master

[48] Pursuant to Vaccine Rule 11(a), the parties may expedite entry of judgment by each filing (either jointly or separately) a notice renouncing their right to seek review.