In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 19-626V

P.J.,

Petitioner,

v.

SECRETARY OF HEALTH AND HUMAN SERVICES,

Respondent.

Special Master Horner

Filed: January 3, 2025
Refiled as Redacted: September 2, 2025

Danielle Anne Strait, Mctlaw, Seattle, WA, for petitioner.
Zoe Wade, U.S. Department of Justice, Washington, DC, for respondent.

DECISION[1]

On April 26, 2019, petitioner filed a petition under the National Childhood Vaccine Injury Act, 42 U.S.C. § 300aa-10, *et seq.* (2012),[2] alleging that she suffered a cerebrovascular injury as a result of a meningococcal vaccine administered on August 11, 2016. (ECF No. 1.) For the reasons set forth below, I conclude that petitioner is *not* entitled to an award of compensation.

I. Applicable Statutory Scheme

Under the National Vaccine Injury Compensation Program, compensation awards are made to individuals who have suffered injuries after receiving vaccines. In general, to gain an award, a petitioner must make a number of factual demonstrations, including showing that an individual received a vaccination covered by the statute; received it in the United States; suffered a serious, long-standing injury; and has

[1] When this decision was originally filed the undersigned advised his intent to post it on the United States Court of Federal Claims' website, and/or at https://www.govinfo.gov/app/collection/uscourts/national/cofc, in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2018) (Federal Management and Promotion of Electronic Government Services). In accordance with Vaccine Rule 18(b), petitioner filed a timely motion to redact certain information. This decision is being reissued with petitioner's name reduced to initials. Except for those changes and this footnote, no other substantive changes have been made. This decision will be posted on the court's website with no further opportunity to move for redaction.

[2] All references to "§ 300aa" below refer to the relevant section of the Vaccine Act at 42 U.S.C. § 300aa-10-34.

received no previous award or settlement on account of the injury. Finally – and the key question in most cases under the Program – the petitioner must also establish a *causal link* between the vaccination and the injury. § 300aa-11(c)(1); § 300aa-13(a)(1)(A)-(B).

In some cases, the petitioner may simply demonstrate the occurrence of what has been called a "Table Injury." That is, it may be shown that the vaccine recipient suffered an injury of the type enumerated in the "Vaccine Injury Table," corresponding to the vaccination in question, within an applicable time period following the vaccination also specified in the Table. If so, the Table Injury is presumed to have been caused by the vaccination unless it is affirmatively shown that the injury was caused by some factor other than the vaccination. § 300aa-13(a)(1)(A)-(B); § 300aa-11(c)(1)(C)(i); § 300aa-14(a). In many cases, however, the vaccine recipient may have suffered an injury *not* of the type covered in the Vaccine Injury Table. In such instances, an alternative means exists to demonstrate entitlement to a Program award. That is, the petitioner may gain an award by showing that the recipient's injury was "caused-in-fact" by the vaccination in question. § 300aa-11(c)(1)(C)(ii). In such a situation, the presumptions available under the Vaccine Injury Table are inoperative. The burden is on the petitioner to introduce evidence demonstrating that the vaccination actually caused the injury in question. *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005); *Hines ex rel. Sevier v. Sec'y of Health & Human Servs.*, 940 F.2d 1518, 1525 (Fed. Cir. 1991).

In this case, petitioner has alleged that the meningococcal vaccine caused a cerebrovascular injury, which is not listed on the Vaccine Injury Table relative to the meningococcal vaccine. Therefore, petitioner must meet the burden of proof for establishing causation-in-fact.

The showing of "causation-in-fact" must satisfy the "preponderance of the evidence" standard, the same standard ordinarily used in tort litigation. § 300aa-13(a)(1)(A); *see also Althen*, 418 F.3d at 1279; *Hines*, 940 F.2d at 1525. Under that standard, the petitioner must show that it is "more probable than not" that the vaccination was the cause of the injury. *Althen*, 418 F.3d at 1279. The petitioner need not show that the vaccination was the sole cause but must demonstrate that the vaccination was at least a "substantial factor" in causing the condition and was a "but for" cause. *Shyface ex rel. Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999). Thus, the petitioner must supply "proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury[,]" with the logical sequence being supported by "reputable medical or scientific explanation, *i.e.*, evidence in the form of scientific studies or expert medical testimony." *Althen*, 418 F.3d at 1278 (quoting *Grant ex rel. Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992)). Ultimately, petitioner must satisfy what has come to be known as the *Althen* test, which requires: (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 proximate temporal relationship between vaccination and injury. *Id*.

A petitioner may not receive a Vaccine Program award based solely on his or her assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. § 300aa-13(a)(1). Medical records are generally viewed as particularly trustworthy evidence because they are created contemporaneously with the treatment of the patient. *Cucuras ex rel. 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. § 300aa-13(b)(1). A petitioner may rely upon circumstantial evidence. *See Althen*, 418 F.3d at 1280. The *Althen* court noted that a petitioner need not necessarily supply evidence from medical literature supporting petitioner's causation contention, so long as the petitioner supplies the medical opinion of an expert. *Id*. at 1279-80. While scientific certainty is not required, that expert's opinion must be based on "sound and reliable" medical or scientific explanation. *Boatmon ex rel. J.B. v. Sec'y of Health & Human Servs*., 941 F.3d 1351, 1359 (Fed. Cir. 2019).

Cases in the Vaccine Program are assigned to special masters who are responsible for "conducting all proceedings, including taking such evidence as may be appropriate, making the requisite findings of fact and conclusions of law, preparing a decision, and determining the amount of compensation, if any, to be awarded." Vaccine Rule 3(b)(1). Special masters must ensure each party has had a "full and fair opportunity" to develop the record but are empowered to determine the format for taking evidence based on the circumstances of each case, including having the discretion to decide cases without an evidentiary hearing. Vaccine Rule 3(b)(2); Vaccine Rule 8(a), (d). Special masters are not bound by common law or statutory rules of evidence but must consider all relevant and reliable evidence in keeping with fundamental fairness to both parties. Vaccine Rule 8(b)(1). 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." § 300aa-13(b)(1). The special master is required to consider all the relevant evidence of record, draw plausible inferences, and articulate a rational basis for the decision. *Winkler v. Sec'y of Health & Human Servs.*, 88 F.4th 958, 963 (Fed. Cir. 2023) (citing *Hines*, 940 F.2d at 1528).

II. Procedural History

This case was originally assigned to another special master. (ECF No. 4.) It was reassigned to the undersigned on August 26, 2019. (ECF Nos. 11-12.) Petitioner initially filed medical records marked as Exhibits 1-16. (ECF Nos. 6-7). Respondent then filed a Rule 4 Report recommending against compensation. (ECF No. 13.) Respondent did not dispute the fact of petitioner's alleged cerebrovascular injury, but

disputed any causal connection to her vaccination and further suggested that treatment with sertraline could be a more likely explanation.[3] (*Id*. at 14-16.)

Thereafter, petitioner filed additional medical records (Exs. 17-20) and an expert report by neurologist Ryan Felling, M.D., Ph.D. (Exs. 21-29). (ECF Nos. 15, 21.) Respondent filed responsive reports by vascular neurologist Steven Messé, M.D., and immunologist Ross Kedl, Ph.D. (ECF Nos. 26-27; Exs. A-D.) Petitioner filed a responsive report by Dr. Felling (Ex. 44) and filed a report by immunologist S. Sohail Ahmed, M.D. (Exs. 33-42). (ECF Nos. 32, 35.) The parties then exchanged a further round of reports by all four experts. (ECF Nos. 37-38 (Ex. E (Messé) and Ex. F (Kedl)); ECF Nos. 41-42 (Ex. 45 (Felling) and Ex. 46 (Ahmed)).)

I held a Rule 5 Conference on October 14, 2021. (ECF No. 44.) During the conference, I confirmed that, despite Dr. Ahmed additionally raising the presence of a chronic autoimmune condition, petitioner's claim is limited to her allegedly vaccine-caused focal cerebral arteriopathy. (*Id*. at 1.) I also directed the parties to provide further discussion of four studies likely to be key to petitioner's *Althen* prong one showing (Al Qudah et al., Ex. 23; Kothur et al., Ex. 25; Zughaier et al., Ex. 26; and Macko et al., Ex. 27).[4] *Id.* at 1-2. Following the conference, petitioner filed further medical records. (ECF No. 47; Exs. 49-50.) Thereafter, respondent filed further reports by both of his experts (Ex. G (Kedl) and Ex. H (Messé) and petitioner filed a response by Dr. Ahmed (Ex. 51-52). (ECF Nos. 53-54, 61.)

The parties were instructed to schedule an entitlement hearing, but instead opted to resolve entitlement by written briefs pursuant to Vaccine Rule 8(d). (ECF No. 62.) Petitioner filed a motion for a ruling on the written record on July 28, 2023, which was fully briefed. (ECF Nos. 65, 67, 69.) Thus, this matter is now ripe for resolution as to entitlement. I have concluded that the parties have had a full and fair opportunity to develop the record and that it is appropriate to resolve this case without an entitlement hearing. *See Kreizenbeck ex rel. C.J.K. v. Sec'y of Health & Human Servs*., 945 F.3d 1362, 1366 (Fed. Cir. 2020) (citing *Simanski v. Sec'y of Health & Human Servs*., 671 F.3d 1368, 1385 (Fed. Cir. 2012)); *see also* Vaccine Rule 8(d); Vaccine Rule 3(b)(2).

III. Factual History

a. As reflected in the medical records

Petitioner received the subject meningococcal ("Menactra") vaccination on August 11, 2016, during a primary care encounter. (Ex. 1, p. 7; Ex. 35, pp. 7-8.) At the time of vaccination, petitioner was eighteen years old and presented with a possible yeast infection. (Ex. 1, p. 5.) She reported that she was taking an oral contraceptive

[3] Respondent's experts did not ultimately discuss sertraline as a cause of petitioner's condition and so this issue will not be addressed further.

[4] For Al Qudah et al., only an abstract had been filed. Petitioner subsequently confirmed that no complete article was ever published. (ECF No. 46.)

and Zoloft[5] as prescribed. (*Id.*) Her pre-vaccination medical history was significant for surgery to repair a torn meniscus, anxiety, hair loss/thinning, hematuria, small kidney, familial hematuria, and allergic rhinitis. (*Id.*; Ex. 5.) Petitioner was initially prescribed fluconazole[6] for her suspected yeast infection; however, a subsequent urinalysis showed mild bacterial vaginosis without the presence of yeast, and a new prescription was ordered. (Ex. 1, p. 6; Ex. 5, pp. 94-95.) This primary care appointment took place at some point between 4:00 p.m. and 5:00 p.m. on August 11, 2016. (Ex. 1, p. 5.)

The following day, at around 7:30 p.m. on August 12, 2016, the paramedics were dispatched for a "possible stroke." (Ex. 4, pp. 23, 28.) Earlier in the day, petitioner had been running around and playing soccer. (*Id.* at 23.) She reported that she did not drink any water and had barely eaten throughout the day. (*Id.*) At some point, she decided to go for a swim in the river when she noticed weakness and paralysis on the right side of her body, as well as a cold sensation. (*Id.* at 6, 23.) She was unable to pull herself out of the water and required assistance, prompting the 911 call. (*Id.*) When paramedics arrived, they observed that petitioner could not move the right side of her body at all, and she was aphasic with a droopy mouth on the right side. (*Id.* at 23.) On physical examination, petitioner's skin was noted to be "cool, pink, dry." (*Id.*) After a few minutes, petitioner was able to sit up and was feeling "totally normal." (*Id.*) However, she complained of a headache and reported a recent history of hypertension. (*Id.*) She was transported to the hospital for further evaluation. (*Id.* at 23-25.) It is noted that stroke protocol was initiated but subsequently discontinued after petitioner began feeling normal. (*Id.* at 24.)

While at the hospital, petitioner was evaluated for headache with associated paresthesias, focal weakness, and speech changes, which began approximately one hour prior but had since resolved. (Ex. 4, p. 4.) Her temperature was recorded as 98.9º Fahrenheit, and a review of symptoms was negative for chills or fever. (*Id.* at 5.) Although her vital signs showed mild tachycardia, petitioner was noted to be emotional and somewhat anxious. (*Id.* at 6.) Her neurologic examination was normal, and there was no evidence of leukocytosis or anemia. (*Id.* at 5-7, 16-17.) An EKG showed a normal sinus rhythm and possible left arterial enlargement, and a CT of the head and CT angiogram of the head and neck were unremarkable with no significant abnormalities. (*Id.* at 6-7, 13-16.) During her hospitalization, petitioner reported that she had never experienced a similar episode, she had no complaints, and "she just want[ed] to go home." (*Id.* at 6.) She was given Toradol and Tylenol for her headache and advised to return to the hospital if her symptoms returned. (*Id.* at 7, 18.) Her

[5] Zoloft is the brand name for sertraline hydrochloride, which is an orally administered selective serotonin reuptake inhibitor that is used in the treatment of depressive, obsessive-compulsive, and panic disorders. *Zoloft*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=54076 (last visited Oct. 31, 2024); *Sertraline hydrochloride*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=45550 (last visited Oct. 31, 2024).

[6] Fluconazole is an orally or intravenously administered antifungal medication. *Fluconazole*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=18848 (last visted Oct. 31, 2024).

differential diagnoses included transient ischemic attack, hemiplegic migraine, atypical seizure, and cervical artery dissection despite the absence of neck pain. (*Id.* at 6.) Her diagnoses on discharge were transient paralysis and unspecified headache. (*Id.* at 7.) She was discharged home in a stable condition. (*Id.*)

On August 14, 2016, petitioner presented to the emergency department with a two-day history of headache. (Ex. 9, p. 119.) Upon arrival, petitioner was experiencing a panic attack with heavy breathing and tachycardia. (*Id.*) She reiterated the events of August 12, 2016, and reported that, at the time, her symptoms lasted for approximately 30 minutes. (*Id.*) Petitioner's systolic blood pressure was elevated. (*Id.* at 120.) Intermittent tachycardia was noted but believed to be associated with petitioner's anxiety. (*Id.* at 121.) Her physical and neurologic examinations were normal, and an MRI was considered unnecessary at that time. (*Id.*) Her laboratory testing was essentially unremarkable, and a urine sample was apparently contaminated. (*Id.*) Although it was noted that petitioner was recently treated for a yeast infection, there were no significant urinary symptoms as this time. (*Id.*) Petitioner was again discharged with diagnoses of transient paralysis and headache. (*Id.* at 123.) She was instructed to follow up with a neurologist. (*Id.* at 121, 123.)

On August 17, 2016, petitioner presented to neurologist Brent Burroughs, M.D., for right hemiparesis and aphasia. (Ex. 3, p. 2.) She again reiterated the events of August 12, 2016, and her mother indicated some concern that petitioner's symptoms could be the result of her recent meningococcal vaccination. (*Id.*) She reported that she had been feeling "fine" since her August 14, 2016 hospitalization. (*Id.*) Dr. Burroughs noted that petitioner received the "meningococcal vaccine on 8/11 then developed right hemiparesis and aphasia on 8/12 with an associated headache. This lasted 20 minutes then recurred 2 days later." (*Id.* at 3.) His differential diagnoses included transient ischemic attack, atypical migraine, and panic attack. (*Id.*) An MRI was ordered to determine whether petitioner's oral contraceptive should be switched, and she was directed to follow up after completing the imaging. (*Id.*) Petitioner was prescribed a Medrol (Pak)[7] and tramadol HCL.[8] (*Id.*) However, Dr. Burroughs noted that petitioner's exam was normal with no significant risk factors for stroke. (*Id.*)

Petitioner underwent an MRI on August 23, 2016, which showed "[a]cute ischemic infarct involving the left basal ganglia and left frontal lobe." (Ex. 3, p. 12.) There was also "diminutive flow voids involving the left [middle cerebral artery] distribution as well as the left [internal carotid artery]," which was concerning for underlying vasculopathy or dissection. (*Id.*) Based on these results, a repeat CT

[7] Medrol is an orally administered "synthetic glucocorticoid derived from progesterone" which is "used in replacement therapy for adrenocortical insufficiency and as an anti-inflammatory and immunosuppressant in a wide variety of disorders." *Methylprednisolone*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=31014 (last visited Nov. 4, 2024).

[8] Tramadol HCL is an orally administered opioid analgesic that is used to treat moderate to moderately severe pain. *Tramadol hydrochloride*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=50542 (last visited Nov. 4, 2024).

angiogram was ordered and revealed "[a]bnormal irregular stenoses" of the left middle cerebral artery, anterior cerebral artery, internal carotid artery, and posterior cerebral artery. (*Id.* at 4-5, 14.) The MRI findings suggested an acute ischemic cerebrovascular accident; however, given the subsequent CT angiogram findings and petitioner's age, a vasculitic process was of primary concern. (*Id.* at 5, 8; Ex. 6, p. 18.) Petitioner was subsequently transferred to Oregon Health & Sciences University for further testing. (Ex. 6, p. 18.)

On admission, petitioner reported no new symptoms but described a remitting, bilateral posterior headache with occasional pulsation and associated nausea. (Ex. 6, pp. 18-19.) Although her weakness and sensory changes had resolved, petitioner reported an additional episode of anxiety a few days prior that was accompanied by a recurrence of her initial symptoms, although to a lesser extent. (*Id.* at 39.) It was also noted that petitioner had been taking Zoloft for the past month and had a family history of lupus. (*Id.* at 3, 54.) Her screening bloodwork and initial neurologic exam was normal, and her lupus inhibitor evaluation was negative. (*Id.* at 39-46, 107-08.) Petitioner then underwent a repeat MRI on August 24, 2016, which showed a new focus of acute infarction involving the left anterior commissure superimposed on the previously seen infarction in the left lenticulostriate distribution. (Ex. 3, p. 14.) She also underwent a diagnostic cerebral angiogram that showed improvement in the blood vessels when compared to the prior CT angiogram. (*Id.*; Ex. 6, pp. 19, 30; Ex. 10, p. 105.) These results were believed to be consistent with a possible reversable cerebral vasoconstriction syndrome ("RCVS"). (Ex. 10, p. 105; Ex. 6, p. 19; Ex. 3, p. 14.) Specifically, neuroradiologist Gary Nesbit, M.D., opined that petitioner's "significant resolution over a single day and the overall findings" points to RCVS; however, he was reluctant to administer intra-arterial verapamil[9] due to petitioner's relatively low blood pressure. (Ex. 6, p. 19.)

On August 25, 2016, petitioner presented to neurologist Wayne Clark, M.D. (Ex. 6, p. 2.) Dr. Clark noted that vasculitis had been ruled out due to petitioner's marked improvement without treatment and that petitioner was likely suffering from RCVS "from Zoloft or vaccine." (*Id.* at 4.) He prescribed verapamil and aspirin, as well as magnesium glycinate for her headaches. (*Id.* at 4, 55-56.) Petitioner's discharge diagnosis was reversible vasoconstriction syndrome complicated by stroke, but the cause of the condition remained "unclear." (*Id.* at 55.) She was directed to follow up for additional blood work. (*Id.*)

In late September 2016, petitioner underwent a follow up CT angiogram of her head and neck, which showed left internal carotid artery dissection and improved but diminutive flow within the left middle cerebral artery distribution. (Ex. 5, pp. 106-07.)

[9] Verapamil is an orally or intravenously administered calcium channel blocking agent that dilates coronary arteries and decreases myocardial oxygen demand. *Verapamil hydrochloride*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=52873 (last visited Nov. 5, 2024). When intravenously administered, verapamil is used to treat supraventricular tachyarrhythmias, and when orally administered, it is used in the treatment and prophylaxis of angina pectoris, in the treatment of hypertension, and in the prophylaxis of supraventricular tachyarrhythmias. *Id.*

Thereafter, she presented for a follow up with the stroke clinic and complained of daily headaches, which she described as aching/throbbing and primarily affecting the left side. (*Id.* at 158.) It was noted that petitioner's hypercoagulable labs were unremarkable and her urine tox screen was negative. (*Id.*) It was further noted that her rheumatology labs were unremarkable with the exception of elevated antinuclear antibodies ("ANA") at 1:10240 in a speckled pattern and elevated Sjögren's syndrome antibodies at 420. (*Id.* at 158-59.) Additionally, her lupus anticoagulant and cardiolipin tests were negative, and her neurologic exam was normal. (*Id.* at 159.) Given petitioner's presentation, including her workup thus far and continued headaches despite no new neurologic symptoms, the possibility of cerebral vasculitis was again suggested. (*Id.* at 160.) Lupus versus Sjögren's syndrome was also included in the differential. (*Id.*) Petitioner was referred to a neuroimmunologist for further evaluation. (*Id.*)

On November 2, 2016, petitioner presented to Oregon Health & Science University. (Ex. 12, p. 66.) She denied recurrence of hemiparesis or speech issues but reported continued headaches with associated nausea and fatigue. (*Id.* at 66-67.) She described two instances in which she experienced a rash that quickly resolved with allergy medication. (*Id.* at 67.) Although she had discontinued Zoloft, she continued to take verapamil and Tramadol, as well as Vicodin. (*Id.*) It was noted that RCVS secondary to restarting Zoloft was initially suspected, but persistent stenosis and abnormal labs suggested a rheumatologic diagnosis. (*Id.* at 72.) Sjögren's syndrome was discussed, including its association with leukocytoclastic vasculitis and neurologic symptoms, such a peripheral neuropathy and encephalopathy. (*Id.*) Petitioner's intermittent rash could be cutaneous vasculitis, which is also sometimes associated with Sjögren's syndrome; however, further evaluation for vasculitis was necessary at this juncture. (*Id.*) Regarding the differential diagnosis of vasculitis, it was suggested that petitioner suffered from medium to small vessel vasculitis, rather than primary central nervous system vasculitis, due to her systemic symptoms. (*Id.*) Petitioner was referred to a rheumatologist for further evaluation. (*Id.*)

Petitioner presented for a rheumatology evaluation on November 7, 2016. (Ex. 5, p. 150.) The history of present illness lists that petitioner suffered from two strokes, as evidenced on MRI, but the later stroke was mistakenly believed to be a panic attack. (*Id.*) It is also noted that petitioner experienced random numbness in her fingers that generally lasts 10-30 minutes before spontaneously resolving. (*Id.*) Petitioner also reported general fatigue and weakness. (*Id.*) Although it was observed that petitioner's presentation was not consistent with any systemic autoimmune disorder or other condition, such as Sjögren's syndrome, it was suggested that she could be suffering from drug-induced lupus based on her prior use of Zoloft and declining antibodies following discontinuation of the drug. (*Id.* at 153-54.) However, it was also noted that these antibodies can be found in healthy adults so additional bloodwork was ordered. (*Id.* at 154.) In a follow up email, petitioner's rheumatologist confirmed that her bloodwork did not demonstrate evidence of any of the common systemic autoimmune disorders. (Ex. 12, p. 207.)

A few days later, petitioner presented for a follow up with the stroke clinic at Oregon Health & Science University. (Ex. 10, p. 84.) She reported continued headaches and fatigue. (*Id.*) She also reported a facial rash with associated hives. (*Id.* at 85.) A neurologic exam was normal. (*Id.*) Additionally, her ANA was elevated at 1:1280 and in speckled pattern, her Sjögren's syndrome antibodies were only slightly elevated at 248, and her lupus anticoagulant and anticardiolipin were negative. (*Id.* at 86, 105.) Her normal CSF results ruled out CSF inflammation or vasculitis, and her working diagnoses remained RCVS or drug-induced lupus secondary to Zoloft. (*Id.* at 87.) She was continued on aspirin and magnesium, directed to wean off verapamil, and directed to follow up for repeat imaging. (*Id.* at 87-88.) She was also referred to a headache specialist for further evaluation. (*Id.* at 88.)

Petitioner had a neuroimmunology follow up on January 1, 2017. (Ex. 10, p. 105.) She reported that, in attempting to wean off verapamil, she experienced daily throbbing headaches over the back of the head with associated nausea and photophobia. (*Id.*) It was noted that petitioner was infrequently taking Tramadol and Vicodin, but she was advised that these medications can cause medication overuse headaches. (*Id.* at 107-08.) She was prescribed an increased dose of verapamil and directed to undergo an MRI of the cervical spine to evaluate for a possible cervicogenic component. (*Id.* at 108.) It was also noted that there was "no evidence of a Neuroimmunological problem contributing to her clinical picture" and therefore a neuroimmunology follow up was not necessary at this time. (*Id.*)

Further imaging was performed in February of 2017. (Ex. 9, pp. 11-16.) An MRI of the cervical spine showed no significant central canal and neural foraminal stenosis, and an MRI of the brain showed no evidence of mass, hemorrhage, or acute stroke. (*Id.* at 11, 16.) An MRA of the head was normal with the exception of decreased flow through the left middle cerebral and temporal lobe branches. (*Id.* at 14.)

On February 9, 2017, petitioner presented to neurologist Juliette Preston, M.D., for management of chronic headaches. (Ex. 10, p. 131.) Petitioner described her headaches as throbbing; affecting the back, left side of the head; and associated with nausea, sensitivity to light and sound, fatigue, dizziness, and difficulty concentrating. (*Id.*) However, she reported mild improvement in her headaches after increasing her verapamil prescription. (*Id.*) A neurologic exam was normal. (*Id.* at 133-34.) She prescribed Topamax for her headaches and directed to follow up in two months. (*Id.* at 134.) On February 17, 2017, petitioner presented to the stroke clinic for a follow up. (*Id.* at 146.) She reported significant improvement in her headaches with her new prescription. (*Id.* at 147.) A neurologic exam was normal. (*Id.* at 147-48.) It was noted that the lack of improvement on repeat CT angiogram and MRA did not support a diagnosis of RCVS. (*Id.* at 150.) It was suggested that petitioner could have thrombus or congenital vessel abnormality, although the negative CT angiogram does not support the latter diagnosis. (*Id.*) She was directed to follow up for repeat imaging. (*Id.*)

Petitioner followed up with Dr. Preston on April 17, 2017, and reported reduced headaches with diclofenac.[10] (Ex. 10, p. 162.) She was assessed with "chronic daily migraine headache triggered by vascular event last August." (*Id.* at 163.) She was directed to continue taking her medication as prescribed, to keep a headache diary, to increase her intake of potassium rich foods (to alleviate paresthesia), and to follow up in three months. (*Id.* at 163-64.)

On September 17, 2017, petitioner underwent an MRA of her head, which showed "[n]arrowing of the left M1 segment with decreased number of vessels in the left sylvian fissure," which was consistent with an old middle cerebral artery infarct. (Ex. 13, p. 22.) Petitioner followed up with the stroke clinic on September 22, 2017, and it was noted that her rheumatologist initially believed that her elevated ANA and Sjögren's syndrome antibodies were the result of drug-induced lupus secondary to Zoloft. (Ex. 12, p. 323.) However, her working diagnoses were "RCVS vs drug-induced Lupus vasculitis." (*Id.*) It was noted that petitioner successfully weaned off verapamil without worsening symptoms, that her headaches had improved on topiramate,[11] and that she had not experienced any further episodes of focal neurologic symptoms. (*Id.*) Petitioner's September 17, 2017 MRA showed stable narrowing predominantly affecting the distal left middle cerebral artery. (*Id.*) Her neurologic exam was normal during this encounter. (*Id.* at 324.) Petitioner was assessed with acute ischemic stroke and, based on stable narrowing of the left middle cerebral artery, the etiology of petitioner's condition was suspected to represent drug-induced lupus vasculitis or RCVS. (*Id.* at 325.) Although both working diagnoses were possibly related to petitioner's treatment with Zoloft, drug-induced lupus was favored, given the persistence of vessel narrowing. (*Id.*)

On November 21, 2017, petitioner presented to the emergency department, complaining of headache with associated nausea and vomiting. (Ex. 13, p. 9.) She reported that her headache was "worse than normal and similar to after her stroke." (*Id.*) A neurologic exam was normal, as was a CT scan of the head. (*Id.* at 10-11, 15.) The attending physician neither believed that a repeat MRI was necessary nor suspected an acute repeat or worsening cerebrovascular accident or other intracranial vascular abnormality. (*Id.* at 11.) Petitioner was not in acute distress and was discharged. (*Id.*)

Throughout the rest of 2017, 2018, and 2019, petitioner continued to seek evaluation and care for her headaches. (Ex. 15, pp. 4-10, 33-36, 68-71; Ex. 16, pp. 31-36, 49-52, 96-103; Ex. 32, pp. 105-09.) Her treaters remained puzzled by her presentation, noting that it was not clear why she suffered the cerebrovascular accident.

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[10] Diclofenac potassium is an orally administered "treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis, a variety of nonrheumatic inflammatory conditions, pain, and dysmenorrhea. *Diclofenac potassium*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=69744 (last visited Nov. 6, 2024).

[11] Topiramate is an orally administered anticonvulsant that is used in the treatment of partial seizures. *Topiramate*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=50310 (last visited Nov. 6, 2024).

(*E.g.,* Ex. 15, p. 10; Ex. 16, p. 102.) The consensus seemed to be drug-induced lupus vasculitis related to Zoloft as the suspected etiology of her condition with RCVS appearing less likely as time went on. (*E.g.,* Ex. 15, pp. 36, 70; Ex. 16, pp. 35, 51; Ex. 32, p. 109.) This determination was primarily based on the persistence of vessel narrowing; however, it was repeatedly noted that the continued elevation of ANA and Sjögren's syndrome antibodies following discontinuation of Zoloft was "puzzling." (Ex. 15, pp. 36, 70; Ex. 16, p. 35; Ex. 32, p. 109.) Additionally, while other diagnoses were discussed, such as connective tissue disease, Sjögren's syndrome, Moyamoya disease, and fibromuscular dysplasia, these conditions were considered less likely or not detectable at that time, given petitioner's overall clinical presentation. (Ex. 15, pp. 10, 36, 70-71; Ex. 16, p. 35; Ex. 32, p. 109.)

In early 2020, petitioner returned to the stroke clinic at Oregon Health & Science University. (Ex. 32, pp. 44.) Her ANA and Sjögren's syndrome antibody levels were rechecked and remained stable when compared to the 2017 results. (*Id.*) Petitioner reported a new headache type affecting the left eye and ear, which improved with rest. (*Id.*) She described this headache as including a burning and throbbing sensation, as well as associated nausea. (*Id.*) She further described an episode of dizziness, nausea, diaphoresis, paleness, and generalized weakness that last for approximately one hour and improved after she ate some ice cream. (*Id.*) The suspected etiology of petitioner's condition was lupus vasculitis or systemic lupus. (*Id.* at 46.) At this point, RCVS appeared unlikely in the setting of persistent vessel narrowing and drug-induced lupus appeared unlikely due to consistently elevated ANA and Sjögren's syndrome antibodies following discontinuation of Zoloft. (*Id.*) The etiology of petitioner's new headache type was unclear, but repeat imaging was not ordered in the absence of new focal neurologic symptoms or headache that is both progressive/severe and unresponsive to therapy. (*Id.*)

Petitioner followed up with the stroke clinic on August 6, 2020. (Ex. 34, p. 4.) She reported a headache frequency of 1-2 per week. (*Id.* at 5.) Petitioner's neurologic exam was normal. (*Id.* at 5, 7.) In the assessment, the following was noted:

> Interval imaging showed stable narrowing. . . . Etiology of narrowing is unclear. Suspected initially to be vasculitis process, [lumbar puncture] unrevealing, and there has been no evidence for progression. Did not reverse to suspect RCVS. May represent a Focal Cerebral Arteriopathy (FCA) that can occur in young adults. Etiology of FCA not well understood, but its hallmark is that it is not progressive. There is conjecture that it may be due to a viral infection, and of note patient did have a vaccination the day prior to her event.

(*Id.* at 7.) Repeat vascular imaging was ordered to evaluate for a progressive inflammatory process. (*Id.*) Petitioner underwent an MRA of the head on October 14, 2020, which was normal. (Ex. 49, pp. 102, 107.) During subsequent encounters throughout the rest of 2020, petitioner reported that she was "doing well" overall, and her assessment remained the same. (Ex. 50, pp. 55-57, 90-93.)

In February of 2021, petitioner presented to the stroke clinic and reported that she had experienced a bad migraine that incapacitated her for a week following receipt of a COVID-19 vaccine. (Ex. 50, pp. 34-35.) It was noted that interval imaging showed improved vessel narrowing, but her assessment remained the same. (*Id.* at 37.) Her diagnoses included history of left middle cerebral artery stroke, left middle cerebral artery stenosis, possible Sjögren's syndrome vs. lupus, and chronic refractory migraine. (*Id.* at 36.) There are no further medical records related to petitioner's post-vaccination condition.

IV. Summary of Expert Opinions

a. Petitioner's neurologist, Ryan Felling, M.D., Ph.D.[12]

Dr. Felling opines that petitioner suffered a stroke, and more specifically a form of inflammatory arteriopathy known as a focal cerebral arteriopathy, rather than a RCVS as initially suspected. (Ex. 21, p. 3.) Although he acknowledges that petitioner's initial presentation was consistent with RCVS, the persistence of her condition over time and the focality of her vascular abnormalities are inconsistent with RCVS. (*Id.*) Further, Dr. Felling opines that petitioner's meningococcal vaccination "was at the very least an important contributor" to her arteriopathy. (*Id.*)

Dr. Felling acknowledges that vaccination is generally thought to reduce the risk of stroke (Ex. 21, p. 3), but indicates that this is because the infections they prevent are an even greater risk factor for stroke, which does not suggest vaccines cannot also lead to adverse events more rarely even as they are protective at the population level (Ex. 44, pp. 1-2). In particular, Dr. Felling challenges the methodology of a study by Fullerton et al., cited by Dr. Messé, that reported a protective effect of vaccination against pediatric stroke. (*Id.* at 2 (citing Heather J. Fullerton et al., *Infection, Vaccination, and Childhood Arterial Ischemic Stroke: Results of the VIPS Study*, 85 NEUROLOGY 1459 (2015) (Ex. 28; Ex. A, Tab 6)).) He is also critical of a study by Wintermark et al. because it did not apply the same level of analysis for potentially associating vaccinations to pediatric stroke that it did for infections. (Ex. 45, p. 2 (citing

[12] Dr. Felling received his medical degree and Ph.D. in neuroscience from Penn State University College of Medicine in 2007, before going on to complete a pediatric internship and residency at Children's Hospital of Philadelphia in 2008 and 2009, respectively, and a child neurology residency and vascular neurology fellowship at The Johns Hopkins Hospital in 2012 and 2013, respectively. (Ex. 22, p. 1.) He is board certified in neurology with special qualification in child neurology and vascular neurology, and he maintains an active medical license in Maryland. (Ex. 21, p. 1.) He currently works as an assistant professor in the Department of Neurology at The Johns Hopkins University School of Medicine, director of the Pediatric Stoke Program, and co-director of the Neuro-PICU. (Ex. 22, p. 1.) He also maintains a joint appointment in the Department of Neurology. (*Id.*) In his clinical work, Dr. Felling regularly diagnoses and treats pediatric stroke patients, in addition to patients with a full range of pediatric neurological diseases. (Ex. 21, p. 1.) He also has an active research program related to clinical aspects of pediatric stroke and the basic biological mechanisms of recovery after brain injury in children. (*Id.*) In his research capacity, he has authored 16 original research papers, 10 review articles, 8 case reports, and 6 book chapters. (Ex. 22, pp. 1-4.)

Max Wintermark et al., *Arteriopathy Diagnosis in Childhood Arterial Ischemic Stroke: Results of the Vascular Effects of Infection in Pediatric Stroke Study*, 45 STROKE 3597 (2014) (Ex. A, Tab 10)).)

Dr. Felling indicates that focal cerebral arteriopathy is associated with elevated cytokines including IL-6, IL-8, and CXCL10, which are also induced by the meningococcal vaccine. (Ex. 21, p. 3-4 (citing Kavitha Kothur et al., *Elevation of Cerebrospinal Fluid Cytokine/Chemokines Involved in Innate, T Cell, and Granulocyte Inflammation in Pediatric Focal Cerebral Arteriopathy*, 14 INT'L J. STROKE 154 (2019) (Ex. 25); Susu M. Zughaier, Neisseria Meningitidis *Capsular Polysaccharides Induce Inflammatory Response via TLR2 and TLR4-MD-2*, 89 J. LEUKOCYTE BIOLOGY 469 (2011) (Ex. 26)).) He opines that petitioner's cerebral arteriopathy occurred at a time consistent with a post-vaccination inflammatory response (approximately 24 hours post-vaccination). (*Id.* at 4.) Dr. Felling indicates that multiple studies have shown increased risk of brain infarction within the week following an infection or inflammatory syndrome. (*Id.* (citing Richard F. Macko et al., *Precipitants of Brain Infection: Roles of Preceding Infection/Inflammation and Recent Psychological Stress*, 27 STROKE 1999 (1996) (Ex. 27); Fullerton et al., *supra*, at Ex. 28; Ex. A, Tab 6).) He further suggests that no other likely trigger is evidenced. (*Id.*) In particular, he disagrees with Dr. Messe's suggestion that a yeast infection[13] at the time of vaccination was a likely contributor to petitioner's stroke, stressing that there is no literature available to suggest any causal association between a localized infection and stroke. (Ex. 44, pp. 2-3.) Dr. Felling is critical of Dr. Messé's conclusion that petitioner's stroke was "cryptogenic," *i.e.*, having no cause whatsoever, both because arteriopathy is a defined etiology for stroke and because it merely represents a preconceived bias against her vaccination as a cause of the stroke. (Ex. 45, p. 1.)

b. Respondent's neurologist, Steven Messé, M.D.[14]

Dr. Messé agrees that RCVS is a less likely diagnosis for this petitioner. (Ex. A, pp. 4-5.) He also acknowledges that Dr. Felling's proposed diagnosis of focal cerebral

[13] The immunology experts would subsequently clarify that what is at issue is a bacterial vaginosis, rather than a yeast infection. (Ex. G, p. 9; Ex. 51, pp. 2-4.)

[14] Dr. Messé received his medical degree from the University of Michigan School of Medicine in 1998, before going on to complete an internship, residency, and fellowship at the Hospital of the University of Pennsylvania in 1999, 2002, and 2003, respectively. (Ex. B, p. 1.) He is board certified in neurology and vascular neurology. (*Id.*) He currently works as an associate professor of Neurology at the Hospital of the University of Pennsylvania, University of Pennsylvania School of Medicine. (*Id.*) In that position, he has cared for thousands of stroke patients in the inpatient and outpatient setting, as well as published extensively on issues related to cerebrovascular disease. (Ex. A, p. 1.) Dr. Messé has also served as a member of the Academy of Neurology Guideline Development Committee. (*Id.*; Ex. B, p. 2.) In that capacity, he has authored multiple clinical practice guidelines that are based upon systemic literature reviews requiring critical assessments of study methodology and risk bias. (Ex. A, p. 1.) Additionally, Dr. Messé has served on the Classification of Evidence review panel for *Neurology* and as an ad hoc reviewed on several relevant journals. (*Id.*; Ex. B, pp. 2-3.) In his research capacity, Dr. Messé has authored 84 peer-reviewed research publications, 23 reviews, and 31 editorials, reviews, and chapters, including committee reports. (Ex. B, pp. 8-28.)

arteriopathy is "possible." (*Id.* at 4.) He stresses, however, that stroke is a heterogeneous disorder with numerous pathophysiologic mechanisms and that, especially among children, it is not unusual for even thorough work ups to fail to find any obvious proximate cause of the stroke. (*Id.* at 3.) He cites a study indicating that, among young stroke patients, 24-36% will have no determined cause of their stroke. (*Id.* (citing Jukka Putaala et al., *Analysis of 1008 Consecutive Patients Aged 15 to 49 with First-Ever Ischemic Stroke: The Helsinki Young Stroke Registry*, 40 STROKE 1195 (2009) (Ex. A, Tab 1)).)

Dr. Messé cites several studies for the proposition that vaccines reduce, rather than increase, the risk of stroke, especially in children. (Ex. A, pp. 3-4 (citing Armin J. Grau et al., *Influenza Vaccine is Associated with a Reduced Risk of Stroke*, 36 STROKE 1501 (2005) (Ex. A, Tab 2); A. Niroshan Siriwardena et al., *Influenza and Pneumococcal Vaccination and Risk of Stroke or Transient Ischaemic Attack–Matched Case Control Study*, 32 VACCINE 1354 (2014) (Ex. A, Tab 3); Pai-Feng Kao et al., *Influenza Vaccination Might Reduce the Risk of Ischemic Stroke in Patients with Atrial Fibrillation: A Population-Based Cohort Study*, 8 ONCOTARGET 112697 (2017) (Ex. A, Tab 4); Liam Smeeth et al., *Risk of Myocardial Infarction and Stroke After Acute Infection or Vaccination*, 351 NEW ENG. J. MED. 2611 (2004) (Ex. A, Tab 5; Ex. G, Tab 14); Fullerton et al., *supra*, at Ex. 28; Ex. A, Tab 6; Nancy K. Hills et al., *Recent Trauma and Acute Infection as Risk Factors for Childhood Arterial Ischemic Stroke*, 72 ANNALS NEUROLOGY 850 (2012) (Ex. A, Tab 7)).) Discussing a study by Smeeth et al., Dr. Messé acknowledges that vaccine-preventable infections were found to increase stroke risk but asserts that the separate finding of a decreased risk of stroke within 28 days of vaccination evidences an actual protective effect from vaccination. (*Id.* at 3 (discussing Smeeth et al., *supra*, at Ex. A, Tab 5; Ex. G, Tab 14).) He also highlighted a finding by Fullerton et al. that both prior infection and under-vaccination were risk factors for stroke in children. (*Id.* at 4 (citing Fullerton et al., *supra*, at Ex. 28; Ex. A, Tab 6).) Dr. Messé stresses in particular that the Fullerton study found that children who received the meningococcal vaccine were less likely to experience a stroke. (*Id.* (citing Fullerton et al., *supra*, at Ex. 28; Ex. A, Tab 6).) He also cited two other studies for the proposition that stroke has not been reported as an adverse event associated with the meningococcal vaccine. (*Id.* (citing Hung-Fu Tseng et al., *Safety of Quadrivalent Meningococcal Conjugate Vaccine in 11- to 21-Year-Olds*, 139 PEDIATRICS, January 2017, at 1 (Ex. A, Tab 8); Rongxia Li et al., *Meningococcal Conjugate Vaccine Safety Surveillance in the Vaccine Safety Datalink Using a Tree-Temporal Scan Data Mining Method*, 27 PHARMACOEPIDEMIOLOGY DRUG SAFETY 391 (2018) (Ex. A, Tab 9)).)

In his first report, Dr. Messé notes, in contrast to a complete lack of literature supporting any association between vaccination and the focal cerebral arteriopathy proposed by Dr. Felling, that recent or ongoing infection is the most common explanation for focal cerebral arteriopathy. (Ex. A, pp. 4-5 (citing Fullerton et al., *supra*, at Ex. 28; Ex. A, Tab 6; Catherine Amlie-Lefond et al., *Predictors of Cerebral Arteriopathy in Children with Arterial Ischemic Stroke: Results of the International Pediatric Stroke Study*, 119 CIRCULATION 1417 (2009) (Ex. A, Tab 11)).) Thus, assuming petitioner suffered a focal cerebral arteriopathy, Dr. Messé proposes that

petitioner's ongoing yeast infection would be a more likely cause as compared to vaccination. (*Id.* at 5.) In his second report, however, Dr. Messé indicates in response to Dr. Felling's criticism that "[i]t is probably most accurate to conclude that neither of these issues are likely to have caused her stroke and that this was a cryptogenic stroke, without a clear etiology." (Ex. E, p. 2.)

In his third report, Dr. Messé addresses the four studies referenced in my prior Rule 5 Order and confirms that review of the studies does not change his opinion. (Ex. H.) Dr. Messé suggests that the Al Qudah et al. study never went beyond the abstract phase because it was unlikely to survive peer review, given that it is merely a review of voluntary Vaccine Adverse Event Reporting System (VAERS) submissions with no review for accuracy or relevancy and no comparison to the general population. (*Id.* at 1-2 (discussing Zaid Al Qudah et al., *Stroke After Vaccination in United States. A Report from the CDC/FDA Vaccine Adverse Event Reporting System. [1990-2010] (P01.009)*, NEUROLOGY, Apr. 23, 2012, at 1 (Ex. 23)).) Regarding Kothur et al., Dr. Messé acknowledges that it found higher levels of certain cytokines among those suffering focal cerebral arteriopathy, but stresses that this does not necessarily point to vaccination as the cause of inflammation given that ischemic brain injury is inflammatory in itself and infection-related inflammation is otherwise believed to play a role in focal cerebral arteriopathy. (*Id.* at 2 (discussing Kothur et al., *supra*, at Ex. 25).) Moreover, the study is small, failed to disclose key data, and failed to acknowledge that stroke itself produces an inflammatory response. (*Id.* (citing Klaus Fassbender et al., *Proinflammatory Cytokines in Serum of Patients with Acute Cerebral Ischemia: Kinetics of Secretion and Relation to the Extent of Brain Damage and Outcome of Disease*, 122 J. NEUROLOGICAL SCIS. 135 (1994) (Ex. H, Tab 1)).) Dr. Messé concludes that the Macko et al. study, which found infection and inflammation was more common in the week preceding hospitalization for stroke as compared to controls, is concordant with his opinion. (*Id.* at 3 (discussing Macko et al., *supra*, at Ex. 27.) He defers to Dr. Kedl with respect to the Zughaier et al. study. (*Id.* at 2-3.)

c. Petitioner's immunologist, Sohail Ahmed, M.D.[15]

Dr. Ahmed begins with the premise that the meningococcal vaccine does produce systemic inflammation. (Ex. 42, p. 5.) He notes that the package insert for the Menactra vaccine (the meningococcal vaccine at issue) demonstrates that anorexia, diarrhea, headache, fatigue, malaise, and arthralgia are among the common solicited adverse events following vaccination. (*Id.* (citing Menactra, Meningococcal (Groups A,

[15] Dr. Ahmed received his medical degree from the University of Texas at Houston in 1998 and completed a research fellowship at the National Institutes of Health (NIH), as well as a research fellowship in immunology at MD Anderson Cancer Center in Houston, Texas. (Ex. 43, p. 4; Ex. 42, p. 2.) He returned to the University of Texas to complete a combined residency in general medicine, rheumatology, and rheumatology research. (Ex. 43, p. 4; Ex. 42, p. 2.) Dr. Ahmed is board certified in internal medicine and rheumatology, and he maintains an active medical license in Massachusetts. (Ex. 43, p. 3.) He has held faculty positions in rheumatology and immunology, but he currently works as Senior Vice President of Global Health of Translational Medicine at Galapagos, where he oversees the development of small molecules and vaccines. (*Id.* at 2-3; Ex. 42, pp. 2-3.) He has published 29 original articles, reviews, letters, editorials, and textbook chapters. (Ex. 43, pp. 4-5.)

C, Y. and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine Prescribing Information, [hereinafter Menactra Package Insert], Ex. 36).) According to Dr. Ahmed, these are systemic effects consistent with cytokine production. (*Id.*) Dr. Ahmed acknowledges that Menactra has not been associated with focal cerebral arteriolopathy specifically, but contends that post-marketing experience and epidemiology have difficulty capturing short-duration events with delayed pathologic confirmation (*i.e.*, in this case, petitioner suffered a stroke on August 12, but vasculopathy was not confirmed until August 23). (*Id.* at 8-9.)

As part of the clinical trials, adverse events to Menactra were compared against another meningococcal vaccine, Menomune. (Ex. 42, pp. 5-6.) Menactra had higher rates of systemic adverse reactions. (*Id.* (discussing Menactra Package Insert, *supra*, at Ex. 36, pp. 6-7, 14).) Thus, "[t]his evidence makes it more likely that the petitioner experienced systemic inflammation from Menactra vaccination on August 11, 2016 that would induce levels of inflammation substantial enough to induce focal cerebral arteriopathy." (*Id.* at 6.) Citing a study by McDonald et al., Dr. Ahmed stresses that non-adjuvanted vaccines are capable of producing a detectable systemic cytokine response. (*Id.* at 6-7 (citing Jacqueline U. McDonald et al., *Inflammatory Responses to Influenza Vaccination at the Extremes of Age*, 151 IMMUNOLOGY 451 (2017) (Ex. 37)).) Based on that same study, Dr. Ahmed asserts that a local infection, such as a vaginal infection, is unlikely to similarly produce a systemic cytokine response. (*Id.* at 7-8 (citing McDonald et al., *supra*, at Ex. 37).) Dr. Ahmed is critical of Dr. Kedl for conflating bacterial vaginosis with infections "more broadly." (Ex. 51, pp. 3-4.) He also disagrees with Dr. Kedl's characterization of petitioner's infection as "fulminant." (*Id.* at 2-3.) Therefore, petitioner's vaccination was the more likely cause the of the systemic inflammation that would lead to focal cerebral arteriopathy. (Ex. 42, p. 8.)

Dr. Ahmed acknowledges that, in petitioner's own case, there is a lack of evidence of symptoms consistent with a systemic cytokine response, such as fever, aches, and flu-like symptoms, but stresses that, at the time of petitioner's focal cerebral arteriolopathy, petitioner was swimming in a cold river and was then treated with acetaminophen, which is anti-inflammatory. Both of these factors could help explain the absence of such symptoms, especially fever. (Ex. 42, p. 7; Ex. 46, pp. 5-6; Ex. 51, pp. 8-9.) He opines that petitioner's stroke occurred within an appropriate temporal window for an inference of causation. (Ex. 42, pp. 6-8.) That is, her stroke occurred about 27 hours post-vaccination and the McDonald study showed that post-vaccination cytokine elevations plateau at about 24 hours. (*Id.*)

In his final report, Dr. Ahmed addresses the four papers referenced in my Rule 5 Order. (Ex. 51, pp. 4-8.) Dr. Ahmed defends reliance on the Al Qudah et al. abstract because it is regularly cited, suggesting the authors' statements are generally viewed as supported by the cited data, and the abstract was presented at a neurology conference, which includes its own form of review and scrutiny. (*Id.* at 4-5 (discussing Al Qudah et al., *supra*, at Ex. 23).) He asserts that the Kothur et al. study does support an inflammatory milieu in focal cerebral arteriopathy. (*Id.* at 5-6 (discussing Kothur et al., *supra*, at Ex. 25).) Whereas Dr. Kedl had cited a study by Li et al. as refuting the

Zughaier study, Dr. Ahmed opines that the Li authors do not reach the conclusion suggested by Dr. Kedl, namely that the meningococcal vaccine did not reliably induce an inflammatory response. (*Id.* at 6-7 (discussing Zughaier, *supra*, at Ex. 26; Shuzhao Li et al., *Molecular Signatures of Antibody Responses Derived from a Systems Biology Study of Five Human Vaccines*, 15 NATURE: IMMUNOLOGY 195 (2014) (Ex. C, Tab 5)).) To the extent Dr. Kedl endorsed the Macko et al. study initially filed by petitioner as further evidence that infections can cause focal cerebral arteriopathy, Dr. Ahmed again stresses the distinction between localized bacterial vaginosis and other types of infections, stressing that Macko et al. examined respiratory infections, rather than infections of the vaginal tract. (*Id.* at 7-8 (discussing Macko et al., *supra*, at Ex. 27).) Dr. Ahmed also expresses broader disagreement with Dr. Kedl regarding the relative value of different types of control groups in vaccine studies. (*Id.* at 9-10; Ex. 46, pp. 2-4.)

Dr. Ahmed additionally indicates that petitioner separately developed an undifferentiated connective tissue disease post-vaccination. (Ex. 42, p. 10.) However, petitioner has not pursued any claim that this represents a compensable injury. (ECF No. 44; *see also* ECF Nos. 1, 65, 69.)

d. Respondent's immunologist, Ross Kedl, M.D.[16]

Dr. Kedl opines that there is not reliable scientific evidence to support a connection between the subject vaccination and petitioner's condition. (Ex. F, p. 8.) He prefaces his discussion by noting that the association between vaccination and prevention of stroke is well established in the literature. (Ex. C, p. 2; Ex. G, p. 9 (citing Smeeth et al., *supra*, Ex. A, Tab 5, Ex. G, Tab 14; Mitchell S. V. Elkind et al., *Infectious Burden and Risk of Stroke: The Northern Manhattan Study*, 67 ARCHIVES NEUROLOGY 33 (2010) (Ex. G, Tab 3); Jaume Roquer et al., *Previous Infection and Stroke: A Prospective Study*, 33 CEREBROVASCULAR DISEASE 310 (2012) (Ex. G, Tab 12); Fullerton et al., *supra*, Ex. 28, Ex. A, Tab 6).) Because strokes have been associated with infection and vaccines prevent infections, it follows that vaccination prevent strokes. (Ex. C, p. 2; Ex. G, pp. 9-10 (citing Nadine McCrea et al., *Genetic and Environmental Associations with Pediatric Cerebral Arteriopathy: Insights into Disease Mechanisms*, 50 STROKE 257 (2019) (Ex. G, Tab 10)).) For example, observational studies have found no increased risk of stroke following influenza, tetanus, or pneumococcal vaccinations. (Ex. G, p. 9 (citing Smeeth et al., *supra*, *Ex*. A, Tab 5; Ex. G, Tab 14).)[17]

[16] Dr. Kedl received his Ph.D. in pathobiology from the University of Minnesota Medical School in 1997, before going on to complete a post-doctoral fellowship at Howard Hughes Medical Institute in 2001. (Ex. D, p. 1.) Dr. Kedl went on to be the Senior Immunologist in the Immune Response Modifier program at 3M pharmaceuticals. (*Id.* at 2; Ex. C, p. 1.) Since joining the faculty at the University of Colorado in 2004, Dr. Kedl has maintain an NIH funded research program centered on the biology of vaccine adjuvants and their capacity to induce robust and enduring cellular immunity. (Ex. D, p. 2; Ex. C, p. 1.) Dr. Kedl has authored 72 peer-reviewed publications, 14 invited reviews and commentaries, and 2 book chapters. (Ex. D, pp. 12-20.)

[17] Dr. Kedl asserts that the lack of association between stroke and pneumococcal vaccination is significant because, like the meningococcal vaccine, the pneumococcal vaccine is a carbohydrate-based vaccine. (Ex. G, p. 9.)

Although Dr. Kedl concedes that the Menactra vaccine may induce some degree of inflammation on rare occasion in a rare individual, he contends that the Menactra vaccine cannot reliably induce the level of systemic inflammation necessary to play a causal role in the etiology of petitioner's condition. (Ex. C, pp. 3-5; Ex. F, p. 6.) The Menactra vaccine contains antigens (molecular targets against which an immune response should be generated) in the form of polysaccharides associated with four different strains of meningococcus and diphtheria toxoid conjugated to polysaccharides, but no added adjuvant. (Ex. C, pp. 3-4.) The inclusion of diphtheria toxoid and lack of added adjuvant suggests that the diphtheria toxoid conjugation can "make up for the usual need for an adjuvant, thereby bypassing the need for an acute inflammatory response." (*Id.* at 4 (citing Michael Bröker et al., *Factors Contributing to the Immunogenicity of Meningococcal Conjugate Vaccines,* 12 HUMAN VACCINES & IMMUNOTHERAPEUTICS 1808 (2016) (Ex. C, Tab 1; Ex. G, Tab 1)).) Dr. Kedl further opines that the lack of adjuvant in the Menactra vaccine suggests that there was "no corresponding or consequent innate immune activation sufficient for the arterial pathology diagnosed." (*Id.*) Additionally, the meningococcal capsular polysaccharides that are used in the vaccine are subject to a process that removes any acute inflammatory capacity, likely through depolarization of the carbohydrates into oligomers. (*Id.* (citing Bröker et al., *supra*, at Ex. C, Tab 1).) Dr. Kedl disagrees with Dr. Ahmed's reliance on the study by McDonald et al., noting that the study involved the flu vaccine, which contains minor constituents that are "widely speculated" to induce some minimal degree of inflammation as a way to promote immunity without the help of any additional adjuvants. (Ex. F, pp. 4-5 (discussing McDonald et al., *supra*, at Ex. 37).) He also observes that there was a noted elevation in only 4 out of 27 cytokines studied and suggested that the findings of post-vaccination inflammation in a mouse model may not be especially useful for predicting post-vaccination inflammation in humans. (*Id.*) Instead, Dr. Kedl cites a study showing that Menactra did not reliably induce an inflammatory response when examined *in vitro* and *in vivo*. (*Id.* at 5 (citing Li et al., *supra*, at Ex. C, Tab 5); Ex. C, p. 4.)

Dr. Kedl acknowledges that petitioner's symptoms do not necessarily exclude systemically elevated cytokines; however, he notes that petitioner did not display any symptoms that are typically associated with vaccine-induced inflammation, including fever. (Ex. C, p. 5; Ex. F, p. 5.) Of the systemic adverse events that are typically associated with vaccination (*e.g.*, fever, malaise, irritability, headache, arthralgia, fatigue), only fever was reliably linked to vaccination. (Ex. F, pp. 3, 5-6 (citing Martti Virtanen et al., *Day-to-Day Reactogenicity and the Healthy Vaccinee Effect of Measles-Mumps-Rubella Vaccination*, 106 PEDIATRICS, no. 5, Nov. 2000, at 1 (Ex. F, Tab 3)).) Dr. Kedl opines that "it is inconceivable that levels of secondary inflammatory mediators sufficient for the induction of focal cerebral arteriopathy" could have been induced in the complete absence of symptoms, such as fever, aches, and flu-like symptoms, that are most associated with elevated cytokine production. (Ex. C, p. 5 (citing Stephanie C. Eisenbarth et al., *Crucial Role for the Nalp3 Inflammasome in the Immunostimulatory Properties of Aluminum Adjuvants*, 453 NATURE 1122 (2008) (Ex. C, Tab 4); Amy S. McKee et al., *Alum Induces Innate Immune Responses Through Macrophages and*

Mast Cell Sensors, but These Sensors are not Required for Alum to Act as an Adjuvant for Specific Immunity, 183 J. IMMUNOLOGY 4403 (2009) (Ex. C, Tab 6); Natalia Muñoz-Wolf & Ed C. Lavelle, *A Guide to IL-1 Family Cytokines in Adjuvanticity*, 285 FED'N EUR. BIOCHEMICAL SOC'IES J. 2377 (2018) (Ex. C, Tab 7)).) In his supplemental report, Dr. Kedl cautions against overreliance on the reporting of specific symptoms, as local side effects could be unrelated to any inflammatory response to the constituents of the vaccine. (Ex. F, pp. 2-4.) He explains that the study contained within the package insert for the Menactra vaccine and relied upon by Dr. Ahmed did not contain a placebo, making it difficult to determine what side effects can be reliably related to vaccination. (Ex. F, pp. 2-3; Ex. G, pp. 5-6.)

Dr. Kedl opines that the relationship between the subject vaccination and onset of petitioner's symptoms is mere coincidence. (Ex. C, p. 5.) He observes that petitioner's symptoms were also in close temporal proximity to onset of bacterial vaginosis and suggested that she had a genetic predisposition to immune overactivation as evidenced by elevated autoantibodies. (*Id.* at 6; Ex. G, p. 9.) He explains that, given the available scientific information connecting a broad spectrum of infections with stroke, petitioner's prior infection is "a far more likely, however implausible, cause than the alleged vaccine," though he admits that any relationship between the vaginosis and stroke is speculative. (Ex. F, p. 7; Ex. C, p. 6.)

Finally, Dr. Kedl addresses the four papers referenced in my Rule 5 Order. (Ex. G, pp. 1-4.) Regarding Al Qudah et al., he explains that the abstract used VAERS data, which is a passive surveillance system that may inappropriately conflate correlation with causation and is not peer-reviewed or verified by a subsequently published, peer-reviewed paper. (*Id.* at 1 (citing Al Qudah et al., *supra*, Ex. 23).) Dr. Kedl describes Kothur et al. as a "highly preliminary study" as the number of control samples was insufficient to make any concrete causal claims. (*Id.* at 2 (citing Kothur et al., *supra*, at Ex. 25).) Moreover, none of the inflammatory factors observed in the study were identified in petitioner. (*Id.*) Dr. Kedl acknowledges that data contained in the Zughaier study is relevant because capsular polysaccharides from *N. meningitidis* can stimulate some innate immune receptors; however, the capsular polysaccharides studied were not the same as those used in preparation of the polysaccharides in the Menactra vaccine; the experiment utilized human and mouse cell lines, rather than actual immune cells; and the capsular polysaccharides were not administered *in vivo* to determine the biological relevance of the purported inflammatory potential. (*Id.* at 2-3 (citing Zughaier, *supra*, at Ex. 26).) Finally, Dr. Kedl stresses the relevance of the article by Macko et al. because, while the majority of the infections studied were upper respiratory infections, a broad range of inflammatory events were documented, suggesting that other types of infections may be associated with stroke, which Dr. Kedl explains is more evidence of a connection between petitioner's bacterial infection and her vascular pathology. (*Id.* at 3-4 (citing Macko et al., *supra*. at Ex. 27).)

V. Analysis

a. Medical theory of causation (*Althen* prong one)

Under *Althen* prong one, petitioner must provide a "reputable medical theory," demonstrating that the vaccine received can cause the type of injury alleged. *Pafford ex rel. Pafford ex rel. v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1355-56 (Fed. Cir. 2006) (quoting *Pafford ex rel. Pafford v. Sec'y of Health & Human Servs.*, No. 01-0165V, 2004 WL 1717359, at *4 (Fed. Cl. Spec. Mstr. July 16, 2004)). Such a theory must only be "legally probable, not medically or scientifically certain." *Knudsen ex rel. Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548-49 (Fed. Cir. 1994). Petitioner may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *See Andreu ex rel. Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1378 (Fed. Cir. 2009) (citing *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1325-26 (Fed. Cir. 2006)). However, "[a] petitioner must provide a 'reputable medical or scientific explanation' for [her] theory. While it does not require medical or scientific certainty, it must still be 'sound and reliable.'" *Boatmon*, 941 F.3d at 1359 (quoting *Moberly ex rel. Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1322 (Fed. Cir. 2010); *Knudsen*, 35 F.3d at 548-49).

As explained in her motion papers, petitioner's medical theory is based on the proposition, advanced by her experts, that cytokines shown to be induced by the Menactra vaccine (IL-6, IL-8, and CXCL10) are also hypothesized to be involved in the development of focal cerebral arteriopathy. (ECF No. 65, p. 26.) This assertion is primarily based on two papers initially cited by Dr. Felling – Kothur et al. and Zughaier, respectively. (*Id.* at 27-28, 30.) At first blush, these two articles do appear to dovetail. However, respondent's experts are persuasive in explaining why they are not ultimately robust or persuasive evidence.

Kothur et al. set out to examine whether inflammation plays any role in the development of focal cerebral arteriopathy. (Kothur et al., *supra,* at Ex. 25.) They examined 32 cytokines and chemokines from cerebrospinal fluid collected from five post-stroke pediatric patients diagnosed with focal cerebral arteriopathy and compared them against three control groups, a group of two patients suffering other forms of stroke; a group of 43 patients with proven inflammatory brain disease, *i.e.*, forms of encephalitis; and a group of 20 negative controls. (*Id.* at 1-2.) They found that most of the cytokines examined were not elevated among the focal cerebral arteriopathy group as compared to the encephalitis group. (*Id.* at 4-5.) However, IL-6, IL-8, CXCL1, and CXCL10, were higher among the focal cerebral arteriopathy group than among the two controls suffering other types of stroke. (*Id*.)

On respondent's behalf, both Drs. Kedl and Messé explained that this study is "highly preliminary," especially given the small number of control samples. (Ex. G, p. 2; Ex. H, p. 2.) Dr. Messé further observed that the study's findings are of limited significance with regard to causation, given that other literature has demonstrated that

ischemic brain injury itself leads to an inflammatory response. (Ex. H, p. 2 (citing Fassbender et al., *supra*, at Ex. H, Tab 1).) Fassbender et al., as cited by Dr. Messé, took serial cytokine measurements from peripheral blood samples of acute cerebral ischemia patients and found increasing elevations in cytokines subsequent to onset that correlated to lesion volume. (Fassbender et al., *supra*, Ex. H, Tab 1, pp. 1, 4.) The Fassbender authors acknowledged that stroke can often be caused by infection, which can generate proinflammatory cytokines, but concluded that the increase in cytokines following onset allowed for a "high probability attribution" of the cytokines to the lesion itself. (*Id*. at 4.) Respondent's expert's criticisms of the Kothur et al. study are consistent with the limitations acknowledged by the study authors themselves. Kothur et al. indicated that "[e]ven though the cyto/chemokine elevation is higher in [focal cerebral arteriopathy] compared to non-[focal cerebral arteriopathy] stroke, it is difficult to differentiate if these elevated inflammatory markers are causally associated with the arteriopathy, or secondary to the infarct itself due to the small sample sizes in both groups." (Kothur et al., *supra*, at Ex. 25, p. 5.) They conclude that, absent a larger study, their study is inadequate to determine whether their observations have specificity as biomarkers of focal cerebral arteriopathy. (*Id*.)

Petitioner has not offered any additional evidence to support a causal relationship between the specified cytokines and focal cerebral arteriopathy or stroke. Focal cerebral arteriopathy is an increasingly recognized cause of pediatric ischemic stroke. (Kothur et al., *supra*, at Ex. 25, p. 1; Amlie-Lefond et al., *supra*, at Ex. A, Tab 11, p. 1.) However, though believed to be inflammatory, the pathophysiology of condition is otherwise not well understood. (Kothur et al., *supra*, at Ex. 25, pp. 1-2; Wintermark et al., *supra*, at Ex. A, Tab 10, p. 3.) Apart from citation to Kothur et al., petitioner's experts acknowledge that there is a lack of medical literature associating focal cerebral arteriopathy or stroke with Menactra vaccination. (Ex. 42, pp. 8-9; Ex. 44, p. 2.) Although Macko et al. hypothesized that non-infectious causes of inflammation may be predisposing factors to stroke, that paper only involved patient questionnaires, with no measurement of purportedly causal cytokines or any significant discussion of pathophysiology. (Macko et al., *supra*, at Ex. 27.) Moreover, the non-infectious causes of inflammation observed by the study related to other types of inflammatory syndromes, such as gout exacerbation, psoriasis, and urticaria. (*Id*. at 4.) No instances of vaccination preceding stroke were reported. (*Id*. at 9-10.)

Dr. Ahmed opines that the vaccine can cause "clearly systemic effects," such as anorexia, diarrhea, headache, fatigue, malaise, and arthralgia, as evidenced in the package insert. (Ex. 42, p. 5 (citing Menactra Package Insert, *supra*, at Ex. 36).) He explains that these common adverse events "typically occur through the production of cytokines at the local site that are transmitted systemically" and further notes increased events following vaccination with Menactra, when compared to a different formulation of meningococcal vaccine, demonstrating the potency of the Menactra vaccine and its ability to induce systemic inflammation. (*Id.*) However, this is not a substitute for some kind of demonstration that the Menactra vaccine can cause focal cerebral arteriopathy in particular. Even acknowledging that the vaccine can induce some inflammatory immune response, mere invocation of a vaccine's intended immune response is not in

and of itself sufficient to carry petitioner's burden under *Althen* prong one. *See Elvira ex rel. D.E. v. Sec'y of Health & Human Servs.*, No. 17-531V, 2024 WL 4966035, at *20 (Fed. Cl. Spec. Mstr. Nov. 6, 2024); *Vanore v. Sec'y of Health & Human Servs.*, No. 21-0870V, 2024 WL 3200287, at *18 (Fed. Cl. Spec. Mstr. May 31, 2024); *Kalajdzic ex rel. A.K. v. Sec'y of Health & Human Servs.*, No. 17-792V, 2022 WL 2678877, at *23 (Fed. Cl. Spec. Mstr. June 17, 2022), *mot. for rev. den'd*, No. 17-792V, 2024 WL 4524777 (Fed. Cl. Oct. 18, 2024), *aff'd*, No. 2023-1321, 2024 WL 3064398 (Fed. Cir. June 20, 2024); *Cordova v. Sec'y of Health & Human Servs.*, No. 17-1282V, 2021 WL 3285367, at *17 (Fed. Cl. Spec. Mstr. June 23, 2021). There must be some additional evidence linking the vaccine's immune response to the pathology of petitioner's actual condition. Given the limitations of the Kothur study, Dr. Ahmed's reliance on other types of reported adverse events following Menactra vaccination, as discussed in post-marketing experience, is unpersuasive as any evidence that the inflammatory response to vaccination can produce focal cerebral arteriopathy in particular. (Ex. 42, pp. 5-6 (citing Menactra Package Insert, *supra*, at Ex. 36).)

Zughaier did find that capsular polysaccharides from *N. meningitis* infection induced *inter alia* IL-6, IL-8, and CXCL10 in human macrophage-like cells. (Zughaier, *supra*, at Ex. 26, p. 6.) Again, however, as a threshold matter, the potential value of this study is dependent on acceptance of the Kothur study as persuasive evidence that these particular cytokines are causally important in the development of focal cerebral arteriopathy. Yet, for the reasons discussed above, it is not. Thus, even if fully credited, the Zughaier findings are insufficient to support a theory of causation consistent with petitioner's burden of proof. Moreover, although Dr. Kedl concedes on behalf of respondent that it may be possible for non-adjuvanted vaccines to "induce some degree of inflammation on exceptionally rare occasions that may be detectable in an exceptionally rare individual," he disputes the ability of the Menactra vaccine to produce a robust inflammatory response in general. (Ex. F, pp. 4-5.) He explains that the Menactra vaccine is a non-adjuvanted vaccine that contains meningococcal polysaccharide capsule antigens that are conjugated to diphtheria toxoid and subjected to a process of purification and chemical modification that removes inflammatory potential. (Ex. C, pp. 3-4; Ex. G, p. 3 (citing Bröker et al., *supra*, at Ex. C, Tab 1).) Thus, Dr. Kedl raises additional criticism of the Zughaier study. (Ex. C, p. 4; Ex. G, p. 9.) Most notably, Dr. Kedl observes that the Zughaier findings are based on capsular polysaccharides from the *N. meningitis* bacteria that are not equivalent to those used in the vaccine, which lack the lipooligosaccharide that is key to the virulence of meningococcal infections. (Ex. G, p. 2.) Thus, he contends that the resultant inflammatory response to the capsular polysaccharides studied by Zughaier is not comparable to what would be expected following vaccination with Menactra. (*Id.* at 3.) For example, Figure 2 within the study compared the two types of capsular polysaccharides and showed that the capsular polysaccharides from *N. meningitis* induced levels of IL-8 that far exceeded levels induced by the vaccine-grade meningococcal capsular polysaccharide polymer. (*Id*. (discussing Zughaier, *supra*, at Ex. 26, pp. 6, 18 fig.2).) This is not necessarily surprising, because both parties' experts otherwise agree that infection is a risk factor for stroke and that vaccination potentially has a protective effect at a population level precisely because it prevents

infections. (*Id.* at 10; Ex. 21, p. 3; Ex. 44, p. 1; Ex. A, pp. 3-4; Ex. C, p. 2.) Even assuming *arguendo* that pro-inflammatory cytokines were implicated in the pathogenesis of focal cerebral arteriopathy as discussed by Kothur et al., then it would still stand to reason that the immune response to vaccination must constitute a lesser risk than infection if a protective effect is potentially observable. *Accord Druery v. Sec'y of Health & Human Servs.*, No. 17-1213V, 2023 WL 5094088, at *16 (Fed. Cl. Spec. Mstr. Jul. 11, 2023) (finding that epidemiology establishing a cardio-protective effect of the flu vaccine "does not in itself mean the flu vaccine is incapable of causing acute cardiac events such as myocardial infarction. However, it does mean that the inflammatory response to vaccination cannot be merely equated in its cardiovascular effects with infection."), *mot. rev. den'd* 169 Fed. Cl. 557 (2024).

Although petitioner need not present epidemiology to carry her burden, *Capizzano*, 440 F.3d at 1325-26, it is also true that special master need not ignore relevant epidemiology that undermines petitioner's theory, *D'Tiole v. Sec'y of Health & Human Servs.*, 726 F. App'x 809, 811 (Fed. Cir. 2018). Here, petitioner concedes that epidemiologically vaccination, in general, is either not a risk factor for stroke or is protective against stroke. (Ex. 21, p. 3.) For example, Smeeth et al. found that there was no increased risk of stroke following influenza, tetanus, and pneumococcal vaccination (Smeeth et al., *supra*, at Ex. G, Tab 14, pp. 4, 6), and Fullerton et al. found "only a protective effect of vaccination" notwithstanding the type of vaccine administered (Fullerton et al., *supra*, at Ex. A, Tab 6, pp. 4-6 (explaining that vaccination "of any type" within the prior week was associated with reduced risk of stroke)). Similarly, in a study cohort of over one million meningococcal vaccinations, Li et al. found that there was no statistically significant risk of focal cerebral arteriopathy or stroke following vaccination. (Li et al., *supra*, at Ex. A, Tab 9, pp. 1, 5.) Another study by Tseng et al. found no statistically significant risk of focal cerebral arteriopathy or stroke in a cohort of nearly 49,000 individuals that were vaccinated with the meningococcal conjugate vaccine. (Tseng et al., *supra*, at Ex. A, Tab 8, pp. 1, 5-6.)

Petitioner also cited a paper by Al Qudah et al., which observed 306 cases of stroke from the VAERS[18] database. (Al Qudah et al., *supra*, at Ex. 23.) However, there are several problems with this. First, VAERS represents passive surveillance and is therefore generally viewed skeptically. *Analla v. Sec'y of Health & Human Servs.*, 70 Fed. Cl. 552, 558 (2006); *Ryman v. Sec'y of Health & Human Servs.*, 65 Fed. Cl. 35, 39-40, 43 (2005); *Manville v. Sec'y of Health & Human Servs.*, 63 Fed. Cl. 482, 494 (2004); *Carrington ex rel. Carrington v. Sec'y of Health & Human Servs.*, No. 99-495V, 2008 WL 2683632, at *11 n.19 (Fed. Cl. Spec. Mstr. June 18, 2008), *mot. for rev. denied*, 85 Fed. Cl. 319 (2008); *Jane Doe/03 v. Sec'y of Health & Human Servs.*, 2007

[18] The Vaccine Adverse Reporting System or VAERS is a national early warning system that is co-managed by the Centers for Disease Control and Prevention (CDC) and the U.S. Food and Drug Administration (FDA) and was established to detect possible safety problems in U.S.-licensed vaccines. *About VAERS: Background and Public Health Important*, VAERS, https://vaers.hhs.gov/about.html (last visited Dec. 23, 2024). VAERS is a passive reporting system, meaning that it relies on individuals to submit reports of adverse events following vaccination. *Id.* Anyone can submit a VAERS report. *Id.* As a result, "VAERS is not designed to determine if a vaccine caused a health problem," but it can be "useful for detecting unusual or unexpected patterns of adverse event reporting." *Id.*

WL 2350645, at *4 (Fed. Cl. Spec. Mstr. Aug. 14, 2007). Additionally, and relatedly, only the abstract of this proposed paper was ever produced. Notwithstanding Dr. Ahmed's defense of the abstract (Ex. 51, pp. 4-5), the lack of a complete analysis cannot be ignored, especially in light of the limitations of the VAERS data more generally. Ultimately, petitioner asserts that the Al Qudah abstract stands "simply for the proposition that members of the medical community have suggested stroke as a rare adverse event after vaccination." (ECF No. 65, p. 27.) In that regard, Dr. Felling asserts that the population-level efficacy of vaccines in reducing the occurrence of stroke does not necessarily exclude the possibility of rare cases of vaccine-caused adverse events leading to stroke. (Ex. 44, p. 1; *see also* Al Qudah et al., supra, at Ex. 23, p. 2 (noting that "some" stroke cases "may be triggered by vaccination").) While this point is well-taken, especially given the overall rarity of adverse events following vaccination, *see D'Tiole*, 728 F. App'x at 811 ("[B]ecause vaccine injuries are rare events, the fact that a particular epidemiological study suggests a vaccine is generally safe should not prevent a claimant from prevailing.") (quoting *D'Tiole v. Sec'y of Health & Human Servs.*, No. 15-085V, 2016 WL 7664475, at *29 (Fed. Cl. Spec. Mstr. Nov. 28, 2016), *mot. for rev. denied*, 132 Fed. Cl. 421 (2017), *aff'd*, 726 F. App'x 809 (Fed. Cir. 2018)), Dr. Felling's observation does not amount to affirmative evidence of causation. *See Crutchfield v. Sec'y of Health & Human Servs.*, No. 09-0039V, 2014 WL 1665227, at *14-15 (Fed. Cl. Spec. Mstr. Apr. 7, 2014) (reasoning that "the studies, like *all* epidemiological studies, do not prove that the MMR vaccine can *never* cause Type 1 diabetes. But they offer *no support at all* to Petitioner in carrying *her burden* of showing that the MMR vaccine *can* cause Type 1 diabetes."), *aff'd*, 125 Fed. Cl. 251 (2014); *see also Holmes v. Sec'y of Health & Human Servs.*, 115 Fed. Cl. 469, 486 (2014) ("Absent epidemiological evidence to support causation, it remained the job of petitioner, not respondent, to supply a reputable medical scientific explanation of causation."); *Bender v. Sec'y of Health & Human Servs.*, No. 11-693V, 2018 WL 3679637, at *30 (Fed. Cl. Spec. Mstr. July 2, 2018) ("While I take note of Petitioner's general point that the fact that vaccine injuries are rare means that such epidemiologic evidence cannot conclusively refute a causation theory that is otherwise reliable and/or scientifically plausible, this argument does not diminish the value such evidence can have in appropriate cases."). While not dispositive, epidemiology submitted on this record overall casts at least some doubt on petitioner's assertion that the Menactra vaccine can cause focal cerebral arteriopathy and stroke.

Finally, Dr. Ahmed cites a study by McDonald et al., which found that immunization with and without an adjuvant induced an elevation in various cytokines (McDonald et al., *supra*, at Ex. 37, pp. 4-5), to show that non-adjuvanted vaccines, like the Menactra vaccine, can induce systemic inflammation. (Ex. 42, pp. 6-7.) However, this paper involved the flu vaccine, rather than the Menactra vaccine. (McDonald et al., *supra*, at Ex. 37.) Accordingly, while this paper may add nuance to the experts' discussion regarding the significance of non-adjuvanted vaccine responses, it does not refute Dr. Kedl's opinion that there is a lack of evidence to suggest that the Menactra vaccine, in particular, reliably produces systemic inflammation. (Ex. F, pp. 4-6.) Nor does the McDonald paper meaningfully bolster petitioner's claim in light of the

limitations of the Kothur and Zughaier papers that form the crux of petitioner's *Althen* prong one showing.

Accordingly, petitioner has not preponderantly established that the Menactra vaccine can cause focal cerebral arteriopathy leading to stroke under *Althen* prong one.

b. Logical sequence of cause and effect (*Althen* prong two)

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 1326-27; *Grant*, 956 F.2d at 1147-48. Medical records are generally viewed as particularly trustworthy evidence. *Cucuras*, 993 F.2d at 1528. However, medical records and/or statements of a treating physician's views do not *per se* bind the special master. *See* § 300aa-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 ex rel. Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 745 n.67 (2009) ("[T]here is nothing . . . that mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted."). A petitioner may support a cause-in-fact claim through either medical records or expert medical opinion. § 300aa-13(a). The special master is required to consider all the relevant evidence of record, draw plausible inferences, and articulate a rational basis for the decision. *Winkler*, 88 F.4th at 963 (citing *Hines*, 940 F.2d at 1528).

As previously explained, *Althen* prong one requires a preponderant showing that the subject vaccine can cause the alleged condition while *Althen* prong two requires a preponderant showing that the subject vaccine actually did cause the alleged condition. *Althen*, 418 F.3d at 1278; *Pafford*, 451 F.3d at 1355-56 (approving the special master's querying under *Althen* regarding, first, whether the vaccine "can cause" the alleged injury and, second, whether it "actually caused" the injury in the particular case). Because I am not persuaded that the Menactra vaccine can cause focal cerebral arteriopathy leading to stroke, petitioner necessarily cannot demonstrate that the vaccine did cause the injury at issue in this case. Therefore, *Althen* prong two is addressed below only in the interest of completeness. Of note, nothing in petitioner's own medical history lends any further credence to petitioner's theory under *Althen* prong one. *Capizzano,* 440 F.3d at 1326 (evidence used to satisfy one of the *Althen* prongs can be used to satisfy another *Althen* prong); *but see Althen,* 418 F.3d at 1278 (temporal association alone is insufficient to establish causation).

In briefing, the parties appear to agree that petitioner suffered an infarct and respondent concedes vascular pathology; however, the parties' respective positions deviate regarding whether petitioner has substantiated a diagnosis of focal cerebral arteriopathy. (ECF No. 65, pp. 24-25; ECF No. 67, pp. 22-24.) Because the question of whether petitioner suffered focal cerebral arteriopathy is an integral part of her causal theory, it is appropriate to first determine whether petitioner has substantiated the proposed injury as a prerequisite to the analysis of whether petitioner has carried her

burden under *Althen* prong two. *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1346 (Fed. Cir. 2010). I find that petitioner has preponderantly established a diagnosis of focal cerebral arteriopathy based on the medical records and expert opinion. Petitioner's expert, Dr. Felling, opines that focal cerebral arteriopathy is a more likely diagnosis for petitioner's condition. (Ex. 21, p. 3.) While respondent asserts that Dr. Messé's opinion was limited to concluding that petitioner suffered a cryptogenic stroke of unclear etiology (ECF No. 67, p. 23), Dr. Messé specifically states that a diagnosis of focal cerebral arteriopathy is "possible" and that the other diagnoses explored by petitioner's treaters are "perhaps less likely." (Ex. A, pp. 4-5.) There is also treater opinion, albeit later in the course of her injury, to support a diagnosis of focal cerebral arteriopathy. (Ex. 34, p. 7.) While Dr. Messé makes it clear that no definitive diagnosis is available, I find that petitioner has preponderantly established a diagnosis of focal cerebral arteriopathy.

Petitioner contends that the Menactra vaccine caused systemic inflammation, which led to focal cerebral arteriopathy and, ultimately, stroke. As previously indicated, focal cerebral arteriopathy has been recognized as a cause of stroke in pediatric patients and is believed to have an inflammatory etiology. (Kothur et al., *supra*, at Ex. 25, p. 1; Amlie-Lefond et al., *supra*, at Ex. A, Tab 11, p. 1; Wintermark et al., *supra*, at Ex. A, Tab 10, p. 4.) However, despite opining on an inflammatory mechanism, Dr. Ahmed concedes that there is a lack of medical record evidence of symptoms that are generally associated with a systemic cytokine response, such as fever, aches, and flu-like symptoms. (Ex. 42, p. 7; Ex. 46, pp. 5-6.) Dr. Kedl asserts that it is unlikely that petitioner could suffer from systemic inflammation that was sufficient to invoke focal cerebral arteriopathy leading to stroke in the absence of other symptoms that are consistent with systemic inflammation. (Ex. C, p. 5 (citing Eisenbarth et al., *supra*, at Ex. C, Tab 4; McKee et al., *supra*, at Ex. C, Tab 6; Muñoz-Wofl & Lavelle, *supra*, at Ex. C, Tab 7); Ex. F, p. 5.) Moreover, he cautions against overreliance on subjective symptoms, such as headache, in favor of objective fever, which he contends is the only commonly reported post-vaccination symptom that has been reliably linked to vaccination.[19] (Ex. F, pp. 3, 5-6 (citing Virtanen et al., *supra*, at Ex. F, Tab 3).) In attempting to overcome this hurdle, Dr. Ahmed offers several explanations that each require at least some degree of speculation. And, in any event, even if crediting Dr. Ahmed's opinion, this allows only a possible explanation for an absence of clinical

[19] A study by Virtanen et al. looked at a series of commonly reported post-vaccination symptoms, including fever, respiratory symptoms, nausea or vomiting, diarrhea, rash, arthralgia, conjunctivitis, staying in bed, drowsiness, irritability, and "other potential symptoms," in pediatric patients. (Virtanen et al., *supra*, at Ex. F, Tab 3, pp. 1-2.) The authors found that fever was the "clearest vaccine-attributable effect." (Virtanen et al., *supra*, at Ex. F, Tab 3, pp. 1, 3-4.) Although Dr. Ahmed does not dispute the findings contained in the Virtanen study, he notes that clinical trials for the Menactra vaccine found injection site pain, headache, and fatigue to be the most common adverse reactions in adolescents aged 11-18 – an age range that is more comparable to petitioner's age at the time of vaccination. (Ex. 42, pp. 5-6.) Headache was not specifically addressed by the Virtanen study. However, despite petitioner's complaints of headache prior to onset of her stroke, this symptom does not play a significant role in petitioner's causal theory as the bulk of her expert's discussion relative to *Althen* prong two concerns her fever or lack thereof. Dr. Ahmed initially associated petitioner's headache with connective tissue disease, but he otherwise treats this symptom as sequela of her injury. (*Id.* at 10; Ex. 51, p. 11.)

evidence supporting his opinion. Dr. Ahmed's explanations would still leave a dearth of evidence affirmatively supporting the application of his theory to the facts of this case. *Accord Baldwin v. Sec'y of Health & Human Servs*., 151 Fed. Cl. 431, 447 (2020) (finding that "Petitioner's experts theorized that the Fluvirin vaccine can induce various inflammatory responses which can lead to cardiac arrest . . . Petitioner was required to prove by a preponderance of the evidence that one of her expert's theories actually occurred . . . Petitioner did not identify anything in her medical records to support any of her exerts' various theories by a preponderance of the evidence.") The Federal Circuit has explained that "[a]lthough probative, neither a mere showing of a proximate temporal relationship between vaccination and injury, nor a simplistic elimination of other potential causes of the injury suffices, without more, to meet the burden of showing actual causation." *Althen*, 418 F.3d at 1278 (citing *Grant*, 956 F.2d at 1149).

First, Dr. Ahmed suggests that petitioner's fever may have been masked by external factors. (Ex. 42, p. 7; Ex. 46, p. 5.) One such factor is a non-steroidal anti-inflammatory medication received in treatment of her condition. (Ex. 42, p. 7; Ex. 46, p. 5.) However, a close reading of the medical records shows that petitioner did not report taking any over-the-counter medications to paramedics upon their arrival (Ex. 4, p. 23); received acetaminophen at the hospital only after her temperature was recorded as normal (*Id.* at 7, 18); and first reported taking ibuprofen prior to onset during a rheumatology appointment approximately three months later (Ex. 5, p. 150).

Dr. Ahmed also suggests that a fever could have been masked by the presumably cold river petitioner was swimming in just prior to onset. (Ex. 42, p. 7; Ex. 46, p. 5.) While this potentially has an attractive logic, it is not sufficiently substantiated. Paramedics noted that petitioner's skin was "cool" and "dry," her temperature was recorded as 98.9˚ Fahrenheit upon admission to the hospital, and there was no observation of fever of chills at any point. (Ex. 4, pp. 5, 23.) Dr. Ahmed opines that petitioner's recorded temperature was "surprisingly warm" given the circumstances, but he does not go so far as to opine that petitioner actually had a fever when she arrived at the hospital. (Ex. 42, p. 7.) He instead asserts that "a slight temperature of 98.9 degrees F when measured 43 minutes later . . . is more likely than not a reflection of a higher temperature prior to swimming that was lowered to 98.9 degrees F after swimming in a cold river."[20] (Ex. 46, pp. 5-6.) However, Dr. Ahmed does not explain why this would not have been accounted for by the treating physicians, given that they were aware of her EMS history and that she had been swimming. (*See* Ex. 4, p. 23-28.)

[20] Of note, Dr. Ahmed appears to have identified the wrong river. Dr. Ahmed cites the USGS Data Grapher website for the Tualatin River, which he suggests "is a way to know exactly what the temperature of the river was that day." (Ex. 46, pp. 5-6 (citing *USGS Data Grapher*, U.S. DEP'T INTERIOR: U.S. GEOLOGICAL SURVEY, https://or.water.usgs.gov/cgi-bin/grapher/graph_setup.pl?basin_id+tualatin&site_id=14207200 (last modified July 6, 2024); Data from U.S. Geological Survey (Water Temperature (˚C) graph): Tualatin River at Oswego Diversion Dam (2021) (Ex. 47)).) He reasons that the Legacy Meridian Park Medical Center is in Tualatin, Oregon, and therefore, the river that petitioner "would have swam in is the Tualatin River," which had a water temperature of 69.9˚ Fahrenheit on August 12, 2016. (Ex. 46, pp. 5-6.) However, there is no mention of the Tualatin River in the medical records. Instead, a triage nurse noted on intake that petitioner was actually swimming in the Willamette River. (Ex. 4, p. 7.)

Finally, Dr. Ahmed suggests that petitioner could have simply overlooked the fever or forgotten to mention a fever to her treaters. (Ex. 42, p. 7.) However, accepting this explanation requires overlooking that treaters took petitioner's temperature within an hour of onset and found it to be normal. (Ex. 4, p. 5.) Additionally, although paramedics initially noted that petitioner was "unable to answer any questions" and was "not acting normally," she was eventually more responsive once her facial paralysis subsided. (*Id.* at 23.) There is no evidence that calls into question petitioner's ability to relay subjective symptoms or medical history to her treaters, especially in light of the fact that she contemporaneously reported other symptoms, such as headache and a recent history of hypertension. (*Id.* at 6-7, 23.) The notion that petitioner was simply oblivious to her own bodily symptoms is obviously speculation.

Petitioner may also satisfy her burden under *Althen* prong two through presentation of medical opinion as contained within her medical records. *Andreu*, 569 F.3d at 1375-76; *Capizzano*, 440 F.3d at 1326 (noting that "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'" (alteration in original) (quoting *Althen*, 418 F.3d at 1280)); *but see* § 300aa-13(b) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder*, 88 Fed. Cl. at 745 n.67 ("[T]there is nothing . . . that mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted."). In the instant case, however, the opinions of petitioner's medical providers are not otherwise helpful in clarifying the cause of her condition. In the only notation addressing the possibility of vaccine causation, petitioner's neurologist suggested that RCVS could have resulted from either Zoloft or the vaccine. (Ex. 6, p. 4.) Her working diagnoses remained RCVS or drug-induced lupus secondary to Zoloft only until focal cerebral arteriopathy was advanced as the primary diagnosis in 2020. (*Compare* Ex. 10, p. 87; Ex. 12, p. 323; Ex. 15, pp. 36, 70-71; Ex. 16, pp. 35, 51; Ex. 32, p. 109, *with* Ex. 34, p. 7.) However, there is no treater opinion causally linking petitioner's focal cerebral arteriopathy to her Menactra vaccination as she alleges.

Accordingly, petitioner has not preponderantly shown that the vaccine did cause her injury under *Althen* prong two.

c. Proximate temporal relationship between vaccination and significant aggravation (*Althen* prong three)

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1278. A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorders etiology, it is medically acceptable to infer causation-in-fact." *de 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 coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id.*; *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 542 (2011), *mot. for recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd*, 503 F. App'x 952 (Fed. Cir. 2013); *Koehn ex rel. Koehn v. Sec'y of Health & Human Servs.*, No. 11-355V, 2013 WL 3214877, at *26 (Fed. Cl. Spec. Mstr. May 30, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

In the instant case, petitioner received the subject Menactra vaccine at approximately 4:00 p.m. on August 11, 2016. (Ex. 1, pp. 5, 7.) At around 7:30 p.m. on August 12, 2016, paramedics were dispatched in response to a 911 call related to petitioner's stroke. (Ex. 4, p. 22.) Thus, onset of petitioner's stroke was around 26-27 hours post-vaccination. Dr. Felling notes increased risk of brain infarction within one week following infectious or inflammatory syndromes. (Ex. 21, p. 4 (citing Macko et al., supra, at Ex. 27; Fullerton et al., supra at Ex. A, Tab 6).) He further notes that that onset of petitioner's focal cerebral arteriopathy within 24 hours of vaccination is consistent with a post-vaccination inflammatory response as fever commonly occurs within 24 hours post-vaccination. (*Id.*) Dr. Ahmed agrees that onset of petitioner's stroke was medically acceptable, reasoning that petitioner's onset aligns with the McDonald study's finding that cytokine elevations plateau at around 24 hours. (Ex. 42, pp. 6, 7-8 (citing McDonald et al., *supra,* at Ex. 37).)

Although respondent's experts do not meaningfully dispute petitioner's contention that onset of stroke approximately 26-27 hours post-vaccination is a medically acceptable timeframe for inferring causation in this case, petitioner cannot carry her overall burden of proof based on third *Althen* prong. Specifically, under *Althen* prong one, petitioner did not preponderantly demonstrate that the Menacta vaccine can produce an inflammatory response that could be implicated as a trigger of focal cerebral arteriopathy or stroke. Additionally, petitioner did not present preponderant clinical evidence of the theorized inflammatory response under *Althen* prong two. Accordingly, while the timing of onset may be consistent with the inflammatory mechanism proposed in this case, a temporal association between vaccination and injury onset is by itself insufficient to prove vaccine causation. *Grant*, 956 F.2d at 1148.

VI. Conclusion

Petitioner has clearly suffered a serious injury, and for that she has my sympathy. However, for all of the reasons described above, there is not preponderant evidence that petitioner's focal cerebral arteriopathy or stroke was caused-in-fact by her Menactra vaccination. Therefore, this case is dismissed.[21]

[21] In the absence of a timely-filed motion for review of this Decision, the Clerk of the Court shall enter judgment accordingly.

IT IS SO ORDERED.

s/Daniel T. Horner
Daniel T. Horner
Special Master