In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 16-1713V

(to be published)

* *	Chief Special Master Corcoran
MARCEL PELLETIER *	
and SARAH PELLETIER, *	
parents of B.P. *a minor*, *	
*	
Petitioners, *	Dated: July 7, 2022
*	
v. *	
*	
SECRETARY OF HEALTH AND *	
HUMAN SERVICES, *	
*	
Respondent. *	
*	
* *	

Ronald Craig Homer, Conway Homer, P.C., Boston, MA, for Petitioners.

Emilie Williams, U.S. Department of Justice, Washington, DC, for Respondent.

ENTITLEMENT DECISION[1]

On December 29, 2016, Marcel and Sarah Pelletier, on behalf of their minor child, B.P., filed a petition for compensation under the National Vaccine Injury Compensation Program (the "Program").[2] Petition (ECF No. 1) at 1. Petitioners allege that a Hepatitis A ("Hep. A") vaccine administered to B.P. on August 14, 2015, caused her to experience a pediatric arterial ischemic stroke due to an inflammatory focal cerebral arteriopathy ("FCA"). An entitlement hearing in the matter was held in Washington, D.C., on November 11, 2021.

[1] This Decision will be posted on the United States Court of Federal Claims' website in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 (2012). **This means the Decision will be available to anyone with access to the internet**. As provided by 42 U.S.C. § 300aa-12(d)(4)(B), however, the parties may object to the published Ruling's inclusion of certain kinds of confidential information. Specifically, under Vaccine Rule 18(b), each party has fourteen (14) days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, the entire Decision will be available to the public in its current form. *Id.*

[2] The Vaccine Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3758, codified as amended at 42 U.S.C. §§ 300aa-10 through 34 (2012) [hereinafter "Vaccine Act" or "the Act"]. Individual section references hereafter will be to § 300aa of the Act (but will omit that statutory prefix).

Having reviewed the record, all expert reports and associated literature, and listened to the experts who testified at the hearing, I hereby deny an entitlement award. As discussed in greater detail below, Petitioners have not preponderantly established that the Hep. A vaccine can cause a pediatric stroke, or that it did likely cause B.P.'s injury.

I. Fact History

Pre-Vaccination History

B.P. was born on August 8, 2013. Ex. 1 at 1. At a routine visit on April 1, 2014, B.P.'s pediatrician, Erik Shessler, M.D., at the Dartmouth Hitchcock Medical Clinic ("DHMC"), noted an asymmetric gluteal cleft. Ex. 4 at 38. A November 2014 MRI showed an asymptomatic thoracic arachnoid cyst "around T5-6" that was not compressing the spine, and did not otherwise reveal evidence of tumor or other concerns. *Id.* at 71, 102–03. On October 17, 2014, B.P. received a first dose of the Hep. A vaccine, plus the measles, mumps, and rubella ("MMR"), and varicella vaccines. Ex. 1 at 1. Twelve days later, on October 29, 2014, B.P. was evaluated for a rash that Dr. Shessler assessed as "likely [a] reaction from MMR vaccination . . .". Ex. 4 at 67. Her medical history was otherwise unremarkable.

Vaccination and Initial Symptoms Presentation

On August 14, 2015, B.P. returned to Dr. Shessler for her two-year-old well-visit. Ex. 4 at 98. Her examination was normal. *Id.* At this visit she received her second Hep. A vaccine dose. *Id.* at 98, 100; Ex. 1 at 1. Mr. Pelletier has averred in a witness statement that in the days following she appeared "very sleepy and irritable." Ex. 11 at 2 (Mr. Pelletier's Declaration, dated December 28, 2016). But there is no medical record corroboration of this contention or recorded medical evidence of a reaction before the next medical encounter.

Thirteen days later, on August 27, 2015, Ms. Pelletier called DHMC and stated that because a specialist previously found a cyst on B.P.'s spinal column, she had been instructed to pay attention to B.P.'s motor functions, and therefore wanted to bring to the attention of medical professionals something she had observed. Ex. 4 at 662. She reported that on August 26, 2015 (a day before the call), she noticed B.P. "didn't want to use her left arm," was "holding her cup different," and "kept her hand in a fist." *Id.* Ms. Pelletier also indicated that B.P. had a temperature of 100 degrees and had one episode of vomiting the day prior (August 25, 2015). *Id.* Mr. Pelletier had noticed similar symptoms on August 25-26, 2015. Ex. 11 at 2–3.

Later that same day, B.P. saw pediatrician Renee Plourde, D.O., for an evaluation of the above-referenced "arm problem." Ex. 4 at 103. Ms. Pelletier once again reported that B.P. had experienced a high temperature and an episode of vomiting on August 25th, and additionally noted

she had slept all day on August 26th. *Id.* at 103. Due to these concerns, B.P. did not go to daycare,[3] but instead stayed at her grandmother's, where she played a game that "used her left arm/hand a lot." *Id.* That night, Ms. Pelletier observed that B.P.'s left leg "seemed 'shaky'" and once again that B.P. was clenching her left hand when holding her cup. *Id.* Ms. Pelletier denied any change in her bowels or bladder, seizure activity, headache, mental status change, cough, congestion, diarrhea, and rash. *Id.* Dr. Plourde proposed that B.P. had possible overuse from playing, noting that B.P. was "[w]ell appearing, afebrile, [and] active." *Id.* at 104. Dr. Plourde felt the history of thoracic arachnoid cyst was likely unrelated and observed no neurological deficits on exam. *Id.*

Ms. Pelletier called DHMC the next day (August 28, 2015), now reporting that B.P.'s symptoms of left-hand clenching remained the same. Ex. 4 at 663. When forced to use her left hand to eat, B.P.'s entire arm shook when she lifted her food to her mouth. *Id.* Additionally, B.P. was reportedly extending only her thumb and one finger, keeping the other fingers curled, although her left leg was moving normally and no longer shaking, and no changes in B.P.'s bladder and bowel control were observed. *Id.* B.P. was otherwise eating well and afebrile. *Id.* Ms. Pelletier was advised to monitor B.P.'s symptoms over the following week to see if there was improvement, but to call the office if symptoms began to worsen. *Id.* at 664–65. Ms. Pelletier called DHMC again on August 29, 2015, and spoke with Kate Essad, M.D., of the neurology service. *Id.* at 664. Dr. Essad "[could not] think of post-infectious condition to present this way," although the description of B.P.'s condition suggested to her no other signs of stroke or vascular insult. *Id.*

Emergency Treatment and Search for Disease Explanation

B.P. was taken to see Dr. Plourde later on the afternoon of August 29, 2015, for follow-up regarding her "arm problem" and continued symptoms. Ex. 4 at 107. Dr. Plourde arranged for B.P. to be seen at the DHMC emergency department ("ED") due to concerns of the previously identified thoracic arachnoid cyst (although her exam was "essential[ly] normal"). *Id.* at 108. Initial records stated that B.P. had experienced a four-day history of "left arm weakness and tremor[s]." *Id.* at 110–12, 218–20. B.P. was admitted to pediatric neurology for observation and a sedated MRI. *Id.* at 112–13. Neurology resident Dr. Essad evaluated B.P., noting that her "[left] arm was flaccid to gravity and she had a tremor due to weakness, a pincer grasp, ataxia with reach, and possible ataxia and hyperreflexia of [left] leg." *Id.* at 220.

The following day, multiple imaging tests were performed—a brain MRI, with and without contrast, brain magnetic resonance angiography ("MRA"), magnetic resonance venography ("MRV"), neck MRA, and an MRI of the cervical spine. Ex. 4 at 299–303. The impression was:

[3] A note from emergency department provider Maia Rutman, M.D., from August 29, 2015, stated that B.P. stayed home on August 26th but was no longer ill. Ex. 4 at 111–12.

> 1. Restricted diffusion involving the right basal ganglia consistent with acute or subacute infarction. Associated with this is elevated cortical signal in the right hemisphere on the diffusion sequence which is not definitely visualized on the other sequences. This does raise the possibility of encephalitis. . . .
>
> 2. The caliber of the right supraclinoid carotid artery and right M1 segment are mildly diminished. . .The prominence [of other arteries] represents hyperemia related to the recent infarction or increased collateral flow because of long-standing diminished flow [in other arteries].

Id. at 300. Neurology attending physician Stephen Mott, M.D., indicated in his progress notes that B.P.'s MRI "showed right basal ganglia involvement secondary to viral encephalitis or acute/subacute vascular infarct." *Id.* at 185. He advised a plan to assess for viral encephalitis, obtain a work-up for a hypercoagulable state, and follow up on Lyme titers. *Id.* Pediatric neurologist Nadim Khalil, M.D., observed that "the distribution appear[ed] much more metabolic and/or infectious as opposed to vascular." *Id.*

B.P. was then transferred to the pediatric intensive care unit ("PICU"). Ex. 4 at 185. A lumbar puncture performed that day showed a white blood cell count of 14, with 92 percent lymphocytes, normal protein, normal glucose, and low/normal lactate. *Id.* at 179–80, 189, 195. Treaters ordered multiple infectious, autoimmune, and metabolic studies, including cerebrospinal fluid ("CSF"), herpes simplex virus ("HSV"), enterovirus, arbovirus, and West Nile PCR studies; Lyme and Bartonella antibody panels; CSF pyruvate and lactate, oligoclonal bands; urine organic acids; serum organic acids; ANA, anti-dsDNA and cardiolipin antibody panels. *Id.* 181–82. All were negative except serum amino acids, as well as arbovirus and West Nile virus antibody panels, the results for which were pending at the time of discharge, but later could not be tested for successfully due to a processing problem. *Id.* at 189, 274. B.P. was also started on anti-herpes medicine, which was discontinued when the relevant test came back negative. *Id.* at 307, 166, 144.

On August 31, 2015, B.P. had a hematology/oncology consult with Jack Van Hoff, M.D. Ex. 4 at 202. Dr. Van Hoff noted in the assessment that "[i]schemic stroke is a rare phenomena in the pediatric population (incidence 13/100000)," with an extensive list of possible causes that included "cerebral arteriopathies, congenital or acquired cardiac disease and sickle cell disease . . . thrombophilia and generalized infections particularly varicella and meningitis, vasculopathies (including Ehlers Danlos, Fabry's disease, homocystinuria), vasospastic disorders, trauma[,] and vasculitis." *Id.* at 208. He noted, however, that a cause is not identified in approximately 20 percent of children with cerebral infarction. *Id.* Dr. Van Hoff recommended testing to rule out homocystinuria but did not recommend an extensive work-up for coagulopathies due to the lack of concerning family history. *Id.*

B.P. was also seen by neurology resident Michael Codini, M.D., and attending physician Timothy Lukovits, M.D, for the chief complaint of a stroke. Ex. 4 at 210–13. Dr. Codini "suspect[ed] that the cortical 'abnormality'. . . [was] artefactual . . . and that the only abnormality [was] the striatal infarction. With the patent [middle cerebral artery] [("MCA")], usually this pattern of infarction means that there was an embolus temporarily occluding the MCA stem with spontaneous recanalization." Ex. 4. at 210–11. Dr. Codini advised looking "for sources of embolism."[4] *Id.*

Later that day, B.P. was also seen by attending physician Peter Wright, M.D., of the infectious disease service whose impression was that B.P. suffered from a "stroke as suggested by MRI which would have its own set of etiologies including endocarditis or coagulation defect or is an aseptic meningitis with 14 cells (98% lymphocytes) and this as a[n] alternative diagnosis on MR." Ex. 4 at 210–11. In terms of an explanation for stroke, Dr. Wright noted that the "only clue from history is the enteric illness in patient and sib[ling]."[5] *Id.* As a result, a pending enterovirus polymerase chain reaction ("PCR")[6] test might yield a firmer diagnosis, but felt no additional tests or antibiotics were necessary. *Id.* Later, B.P. was transferred from the PICU to the medical floor. *Id.* at 169. B.P.'s PCR test was negative. *Id.* at 289–90.

On September 1, 2015, A progress note from Ryan Ratts, M.D., indicated that B.P. exhibited "[s]ome increased stiffness in LLE [lower left extremity] which appear[ed] to be a new finding," and neurology was consulted. Ex. 4 at 161. Given this finding and the concern for possible progression, B.P. was treated "with pulse IV steroids for post-viral vasculitis process." *Id.* It was also noted that B.P. had developed a "popular red rash that began that afternoon on her face, arms, and diaper region." *Id.* at 163. Treaters decided to do a repeat MRI/MRA of her brain and started B.P. on aspirin. *Id.* at 161-62.

B.P.'s case was later reviewed at the cerebrovascular conference at DHMC. Ex. 4 at 168. Dr. Lukovits stated that "the diffuse right hemispheric cortical brightness on [diffuse weighted imaging ("DWI")] does seem to be real and I now suspect that there was partial infarction of the cortex." *Id.* In Dr. Luckovits's view, the imaging "suggest[ed] the possibility of early moyamoya disease but the degree of stenosis seem[ed] too mild to get a low flow infarction and striatal

[4] Embolism is "the sudden blocking of an artery by a clot or foreign material that has been brought to its site of lodgment by the blood current." *See Dorland's Illustrated Medical Dictionary* (33d ed. 2020) at 600 [hereinafter *Dorland's]*.

[5] Ms. Pelletier had told Dr. Wright that B.P.'s illness on Tuesday (August 25th), which featured a low-grade fever and an episode of vomiting, had since spread to her 3.5-year-old sister who also had gastrointestinal symptoms. Ex. 4 at 217.

[6] Enteroviruses are "a genus of viruses of the family Picornaviridae that preferentially inhabit the intestinal tract." *Dorland's* at 620. It can be tested for using a PCR, "a type of rapid nucleic acid amplification of specific DNA or RNA sequences." *Id.* at 1467.

infarction is atypical in moyamoya."[7] *Id.* He recommended "continuing to look for a proximal source of embolism and for viral causes of the pleocytosis that could cause a localized vasculitis of the MCA." *Id.*

A repeat brain MRI and head MRA conducted on September 2, 2015, were reviewed by Aleksey Tadevosyan, MD, of the neurology service, and appeared to show "new restricted diffusion involving the right cerebral peduncle and tracts connecting to the lentiform nucleus to the midbrain suggesting acute Wallerian degeneration." Ex. 4 at 147. Dr. Tadevosyan's assessment was, "[f]ocal angiitis of MCA and lenticulostriate arteries that is post-infectious/vaccination [versus] vague [diagnosis] of 'transient cerebral arteriopathy' also called focal cerebral arteriopathy of childhood which can follow a viral illness." *Id.* at 145. Neurologist Richard Morse, M.D., was in fact "reassur[ed]" by the repeat MRI, "as the previously suspected vertical involvement [did] not appear to have persisted on the updated study." Ex. 4 at 155. Although the Wallerian degeneration gave B.P. "a worse prognosis for recovery, . . . the stroke seem[ed] to be limited to the basal ganglia." *Id.* He also noted that the lenticulostriate vessels were prominent and enlarged, suggestive of a vascular process, leading him to recommend a long-term follow-up vascular study. *Id.*

By September 3, 2015, B.P. was using her left hand more frequently and her leg was not as stiff. Ex. 4 at 143. B.P.'s labs were unremarkable "except for elevated CSF Nucleated Cells (14), which seem[ed] to be consistent with a yet unidentified inflammatory process. . . ." *Id.* Dr. Ratts's assessment of possible etiologies included "viral vasculitis, atypical Moya Moya, less likely to have coagulopathy." *Id.* at 143. A Transcranial Doppler (TCD) ultrasound showed "[m]ean velocities in the RIGHT MCA [that were] higher than the contralateral MCA mean velocities and fall at the threshold for moderate vasospasm near mid segment based on vasospasm diagnostic criteria for an adult." *Id.* at 264. It was noted, however, that "[t]here [was] no established diagnostic criteria for stenosis in a pediatric patient." *Id.* And otherwise the etiology of the presumed stroke remained unknown. *Id.* at 132.

B.P. was discharged from DHMC the next day. Ex. 4 at 129. Her discharge instructions indicated continued use of low-dose aspirin, oral prednisolone, continued PT/OT, and repeat MRI in 3 months. *Id.* at 259–60; 265–66.

Subsequent Treatment

In the course of B.P.'s follow-up treatment, treaters considered different potential explanations for her stroke-like injury, although no consensus was reached. For example, on

[7] Moyamoya disease is a "cerebral ischemia due to occlusion of large arteries at the circle of Willis [a place in the brain where arteries connect], with secondary proliferation of an abnormal network of vessels at the base of the brain, causing progressive neurologic disability; hemorrhage may occur from the abnormal vessels." *Dorland's* at 532.

September 11, 2015, B.P. had a visit with Dr. Shessler. Ex. 4 at 593. He reviewed the hospital records and noted that the cause of her cerebral infarction remained unknown but was "presumabl[y] viral although all studies have been normal." *Id.* He observed significant increased stiffness in her left arm. *Id.*

B.P. underwent an MRI on November 10, 2015, and the radiology report noted "there are areas of evolving encephalomalacia involving the right putamen and superior aspect of the right caudate consistent with evolution of previously seen areas of infarct. There is associated ex vacuo dilatation of the adjacent right lateral ventricle." Ex. 4 at 691. There was no new mass lesion and the cerebral parenchyma elsewhere remained unchanged." *Id.* The impression was "[e]volution of previously seen infarct in the region of the right basal ganglia" and "unchanged appearance of the MRA." *Id.*

By the start of 2016, B.P. appeared to be improving, although she required left-sided braces. Ex. 4 at 627. At this time, she was diagnosed with arteriopathy of childhood. *Id.* at 628. By April 2016, she began to display greater lower left extremity tone as well as progress associated with physical therapy sessions. Ex. 6 at 13. That progress continued through the summer. Ex. 9 at 5,11. Indeed, by August 2016, Dr. Shessler assessed B.P. as a "[h]ealthy 3-year-old female with normal growth and development." *Id.* at 12.

B.P. was evaluated by physiatrist Harry Webster, M.D., at Tufts Physical Medicine and Rehabilitation Musculoskeletal Center on October 28, 2016. Ex. 10 at 2. Her left-hand function was at this time deemed "not back to its baseline," and she was reportedly "falling more than other 3 y[ea]r old children according to parents, but only with [her] brace off." *Id.* Upon examination, her tone was increased in her left arm compared to her left leg. *Id.* The assessment was left-sided hemiplegic cerebral palsy. *Id.* at 3. Recommendations included physical therapy ("PT") and different types of bracing with Botox as a future option. *Id.*

In January 2017, B.P. underwent an initial PT evaluation with Northeast Rehabilitation Health Network in Salem, New Hampshire. Ex. 15 at 8. Her exam revealed increased left-sided upper and lower extremity (LE > UE) with diminished abilities on gross motor developmental skills testing for age for each extremity. *Id.* at 9. Six months later, B.P. had a follow-up visit with Dr. Morse in July 2017, who found that B.P. was progressing with no concerning new developments. Ex. 21 at 9–12. At this time, Dr. Morse noted her history of stroke attributed to arteriopathy of childhood, deeming its cause "presumed post-infectious." *Id.*

Since then, B.P.'s condition has overall remained stable, despite some remaining deficits. On May 28, 2021, B.P. presented for a well-child visit with Dr. Shessler. Ex. 33 at 14. His assessment was "healthy 7 [year old] 9 [month] female with normal growth and development," despite the presence of spastic hemiplegia with increased tone in the left lower extremity and

abnormal gait. *Id*. The plan was to follow up with her orthopedist and try a stimulation device in addition to continued bracing and stretching at home. *Id.* Dr. Shessler also noted that they "[d]iscussed vaccine today, family interested in potentially completing tetanus. . . [B.P.'s] stroke has very appropriately made them more cautious, this occurred temporarily within 2 weeks after 2nd hep A." *Id.* at 15. But this record does not otherwise implicate the vaccine as causal in Dr. Shessler's estimation.

II. Witness Testimony

A. *Petitioners' Expert – Kevin A. Shapiro, M.D., Ph.D.*

Dr. Shapiro, a pediatric vascular neurologist, submitted two expert reports and testified for the Petitioners in support of their contention that the Hep. A vaccine can cause pediatric stroke.[8] *See generally* Tr. at 5–144. Report, dated Sept. 12, 2017, filed as Ex. 17 (ECF No. 27-1) ("Shapiro First Rep."); Report, dated May 20, 2018, filed as Ex. 23 (ECF No. 41-1) ("Shapiro Second Rep.").

Dr. Shapiro attended Harvard University for his undergraduate, doctoral, and postdoctoral degree. *See* Curriculum Vitae, filed Sept. 25, 2017 (ECF No. 27-2) ("Shapiro CV") at 1. He also attended Harvard Medical School for his medical degree. Tr. at 6; Shapiro CV at 1. He then completed his residency at Boston Children's Hospital, Brigham and Women's Hospital, and Massachusetts General Hospital, and a fellowship at the University of California, San Francisco. Tr. at 6–7; Shapiro CV at 1. He is a medical director and director of research at Cortica, a healthcare organization dedicated to the care of children with complex neurodevelopmental disabilities. Tr. at 7. Previously, he served as Assistant Professor of Neurology at the University of California, San Francisco. *Id.* Overall, Dr. Shapiro has treated approximately 200-300 pediatric vascular patients about a third of them have experienced ischemic strokes. *Id.* at 11–12. He has published several peer-reviewed articles, specifically pertaining to pediatric stroke. Tr. at 9; Shapiro CV at 8–12. He is licensed to practice medicine and is board certified in psychiatry and neurology. Tr. at 6; Shapiro CV at 1.

FCA, Dr. Shapiro explained, refers to the narrowing of the distal branches of the internal carotid artery (usually the proximal part of the middle cerebral artery), which supplies blood to a large part of the brain, including the basal ganglia and parts of the cerebral cortex. Tr. at 14. Dr. Shapiro differentiated FCA from a few other arteriopathies, like a transient cerebral arteriopathy or post-varicella infection arteriopathy (which is specifically understood to arise secondary to a varicella/chickenpox infection). *Id.* at 18–25, 41-42, 131. An FCA injury does not articulate a cause or time course but refers to the fact that a portion of the arteries in the brain become diseased,

[8] Dr. Shapiro referred to B.P.'s injury as a stroke or pediatric stroke, a term which appeared interchangeable with the more precise descriptors used by Dr. Cummings (pediatric arterial ischemic stroke or arterial ischemic stroke).

narrowed, or inflamed, which might not resolve (in contrast with a transient cerebral arteriopathy, where the arterial narrowing is due to a focal injury that can soon resolve). *Id.* at 18–19.

When the arterial segments are narrowed, there is limited blood flow, and it predisposes the individual to the formation of a clot, which can subsequently provoke a stroke. Tr. at 14, 138. The disease process affects a relatively focal segment of the cerebral vasculature (always in the same area of the brain). *Id.* at 14. It is not fully understood why that region of the cerebral vasculature is more prone to injury, but science has determined that it is susceptible[9] to a wide variety of diseases that can lead to abnormal coagulation leading in turn to clotting and strokes. *Id.* at 15–16, 29–32, 51–52. Turbulent blood flow, Dr. Shapiro proposed, could contribute to the clot formation in this brain region. *Id.* at 17, 52. Another relevant factor is the pattern of blood flow associated with the internal carotid artery, which supplies blood to the anterior circulation of the brain. *Id.* This artery splits into several branches around the Circle of Willis[10] to provide blood supply to the rest of the brain. *Id*.

FCA accounts for 25-32 percent of strokes in children between the ages of one month to 18 years. Shapiro First Rep. at 1; C. Amlie-Lefond et al., *Predictors of Cerebral Arteriopathy in Children with Arterial Ischemic Stroke: Results of the International Pediatric Stroke Study*, Circulation 1417, 1420 (2009), filed as Ex. 17, Tab B on Oct. 5, 2021 (ECF No. 68-2) ("Amlie-Lefond I"). By contrast, post-varicella arteriopathy may account for up to 44 percent of inflammatory FCA cases in children and adults. Shapiro First Rep. at 1, 3; Amlie-Lefond I at 1421–22; C. Amlie-Lefond & D. Gilden, *Varicella Zoster Virus: A Common Cause of Stroke in Children and Adults*, J. Stroke & Cerebrovascular Diseases 1561, 1563 (2016), filed as Ex. 17, Tab C on Oct. 5, 2021 (ECF No. 68-3) ("Amlie-Lefond II"); S. Lanthier et al., *Post-Varicella Arteriopathy of Childhood: Natural History of Vascular Stenosis*, Neurology 660, 661–62 (2005), filed as Ex. 17, Tab P on Oct. 5, 2021 (ECF No. 69-6) ("Lanthier"); S. Thomas et al., *Chickenpox and Risk of Stroke: A Self-Controlled Case Series Analysis*, Clinical Infectious Diseases 61, 64 (2014), filed as Ex. 17, Tab Y on Oct. 5, 2021 (ECF No. 70-5); K. P. J. Braun et al., *The Course and Outcome of Unilateral Intracranial Arteriopathy In 79 Children with Ischaemic Stroke*, Brain 544, 550 (2009), filed as Ex. 17, Tab F on Oct. 5, 2021 (ECF No. 68-6) ("Braun").

Dr. Shapiro next discussed possible causes of FCA. At the outset, he agreed with Respondent's expert that FCA likely was multifactorial in nature (although risk factors significant to adult stroke, like smoking or hypertension, would not be relevant in a pediatric context). Tr. at

[9] Dr. Shapiro also noted that although most of these diseases occur in childhood, there is some evidence that areas are susceptible to thrombosis and injury throughout a person's life. Tr. at 17.

[10] The Circle of Willis is an area of the brain that connects several arteries, permitting arterial blood flow to one hemisphere of the brain to reach the other hemisphere. *See Huffman v. Sec'y of Health & Hum. Servs.*, No. 07-81V, 2011 WL 995958, at *9 (Fed. Cl. Spec. Mstr. Feb. 28, 2011) (*citing Gray's Anatomy* (S. Standring ed., 40th ed. 2008) at 251–52).

23, 39-40, 191; Shapiro First Rep. at 1, 3; Shapiro Second Rep. at 1. In most cases, the precise trigger for FCA is not identified, and the mechanism that might specifically lead to vasculitis and ischemic stroke is not well understood even after a routine workup. Tr. at 40–41, 135–36; Shapiro First Rep. at 1; Shapiro Second Rep. at 1. Even so, FCA is presumed to occur because of an inflammatory response to infection, and is thus considered a type of vasculitis. Tr. at 23; Shapiro First Rep. at 1; Braun at 555; S. Chabrier et al., *Transient Cerebral Arteriopathy, Postvaricella Arteriopathy, and Focal Cerebral Arteriopathy or the Unique Susceptibility of the M1 Segment in Children with Stroke*, Stroke 2439, 2439 (2016), filed as Ex. 17, Tab H on Oct. 5, 2021 (ECF No. 68-8).

Other reported causes of FCA include dissection, cytomegalovirus, enterovirus, human immunodeficiency virus, and Lyme disease. Tr. at 14–15; Shapiro First Rep. at 1; W-T. Kao et al., *Transient Cerebral Arteriopathy in a Child Associated with Cytomegalovirus Infection*, Child Neurology 1, 2 (2015), filed as Ex. 17, Tab N on Oct. 5, 2021 (ECF No. 69-4) ("Kao") (cytomegalovirus); P. Ribai et al., *Transient Cerebral Arteriopathy in Infancy Associated with Enteroviral Infection*, Eur. J. Paediatric Neurology 73, 75 (2003), filed as Ex. 17, Tab W on Oct. 5, 2021 (ECF No. 70-3) ("Ribai") (enterovirus); W-H. Tsai et al., *Cerebral Infarction Associated with Possible Enteroviral Infection in an Infant*, 45 Acta Paediatric Taiwan 296, 298 (2004), filed as Ex. 17, Tab Z on Oct. 5, 2021 (ECF No. 70-6) ("Tsai") (enterovirus); J. W. Leeuwis et al., *A Child with HIV-Associated Transient Cerebral Arteriopathy*, Aids 1383, 1383 (2007), filed as Ex. 17, Tab Q on Oct. 5, 2021 (ECF No. 69-7) ("Leeuwis") (human immunodeficiency virus); M.G. Cox et al., *Neuroborreliosis Causing Focal Cerebral Arteriopathy in a Child*, Neuropediatrics 104, 106 (2005), filed as Ex. 17, Tab J on Oct. 5, 2021 (ECF No. 68-10) (Lyme disease).[11]

There are thus several external triggering factors that can produce FCA. Dr. Shapiro opined the Hep. A vaccine could represent a similar trigger—although he admitted that *neither* the vaccine *nor* the underlying wild virus are themselves understood by medical science to be so associated. Shapiro First Rep. at 2.

To establish this contention, Dr. Shapiro began by considering the foundational context in which FCA would arise. Reliable science, he maintained, shows that FCA can be mediated by an inflammatory immune response implicating both "arms" of the immune response—the initial, innate response and the subsequent adaptive response. Tr. at 44, 80, 139–41. Dr. Shapiro admitted that it is difficult to outline the mechanism by which FCA occurs. Indeed, even in the context of a prior varicella infection (an accepted FCA cause), the actual virus's presence in the walls of cerebral blood vessels cannot be consistently demonstrated. Shapiro First Rep. at 1. It is thus theorized that this kind of arteriopathy may be the product of immune complex deposition

[11] As Dr. Cummings later pointed out, however, Kao, Ribai, Tsai, and Leeuwis all concluded that a prior direct infection was essential to trigger the initial immune response later culminating in stroke. Tr. at 174; Cummings First Rep. at 10.

secondary to an ongoing infection occurring elsewhere in the body. Tr. at 26–27; Shapiro First Rep. at 1; C. Linnemann, Jr., & M. Alvira, *Pathogenesis of Varicella-Zoster Angiitis in the CNS*, Archives Neurology 239, 239 (1980), filed as Ex. 17, Tab R on Oct. 5, 2021 (ECF No. 69-8).

Dr. Shapiro broke down the process he deemed applicable to this case into two components: a "hypercoagulable" state for the blood, coupled with the deposition of immune complex in reaction to a prior immune stimulation. Tr. at 137–38. A hypercoagulable state, he explained, could arise in an inflammatory context (propagated, for example, by an ongoing infection), and would result a greater propensity to form blood clots. Tr. at 27–28. This would occur not because of an immune reaction against the platelets in the blood (which form clots), but rather from vessel narrowing more generally. *Id.* at 138. Hypercoagulability is a known risk factor for stroke and can be considered permanent or transient. *Id.* at 28–29. The second contributing factor, immune complex deposition, is the product of an immune-mediated response in which immunoglobulins[12] (specifically IgG or IgM)—a kind of antibody—bind to an infectious or viral antigen, forming a "complex." Tr. at 25. This complex can in turn act like an antigen itself, setting off a cascading immune reaction which can instigate subsequent additional inflammation. *Id.* at 25–26, 32–33.

In Dr. Shapiro's opinion, vaccination generally could lay the groundwork for the aforementioned inflammatory context in which these immune processes would unfold. Tr. at 44, 80. Vaccines are known to stimulate the production of inflammatory cytokines (as part of the innate immune response). Although this cytokine stimulation is essential to immunogenicity, it is also likely a contributor to subsequent adverse events. *Id.* at 74, 76–78; Shapiro Second Rep. at 3; A. Batista-Duharte et al., *Progress in Understanding Adjuvant Immunotoxicity Mechanisms*, Toxicology Letters 97, 101–02 (2011), filed as Ex. 23, Tab A on Oct. 5, 2021 (ECF No. 70-8) ("Batista-Duharte"); Y. Kashiwagi et al., *Production of Inflammatory Cytokines in Response to Diphtheria-Pertussis-Tetanus (DPT), Haemophilus Influenza Type B (Hib), and 7-Valent Pneumococcal (PCV7) Vaccines*, Hum. Vaccines & Immunotherapeutics 677, 678, 681 (2014), filed as Ex. 23, Tab G on Oct. 5, 2021 (ECF No. 71-2) ("Kashiwagi").

Kashiwagi, however, only studied literal cytokine increases caused by vaccination, and how this impacts a vaccine's overall immunogenicity in stimulating the adaptive response. S*ee e.g.*, Kashiwagi at 681. Batista-Duharte, by contrast, did no more than theorize about the possibility of vaccine adjuvants contributing to autoimmune conditions. Batista-Duharte at 101-02. Neither article thus goes very far in assisting Petitioners' theory—nor, more fundamentally, did either discuss at all the cytokine-stimulating capacity of the Hep. A vaccine.

Dr. Shapiro did, however, offer some medical literature specifically discussing the immune response generated by the Hep. A vaccine itself. *See e.g.*, J. Melgaço et al., *A Single Dose of*

[12] Immunoglobins are divided into five classes—IgM, IgG, IgA, IgD, and IgE—and defined as any of the structurally related glycoproteins that function as antibodies. *Dorland's* at 909.

Inactivated Hepatitis A Vaccine Promotes HAV-Specific Memory Cellular Response Similar to That Induced by a Natural Infection, Vaccine 3813, 3818 (2015), filed as Ex. 23, Tab J on Oct. 5, 2021 (ECF No. 71-5) ("Melgaço"); C. Scheibenbogen et al., *Interferon-Gamma-Induced Expression of Tissue Factor Activity During Human Monocyte to Macrophage Maturation*, Haemostasis 173, 173–74 (1992), filed as Ex. 23, Tab M on Oct. 5, 2021 (ECF No. 71-8) (emphasizing the mechanisms by which inflammation and the production of pro-inflammatory cytokines can lead to clotting). In some cases, these responses significantly exceed the responses induced by natural infection and can persist for up to 24 months following the administration of a second vaccine dose. Tr. at 75–76; Melgaço at 3818 (indicating that even if the individual is not able to receive a second dose, a first dose is enough to produce a robust response for an immune reaction). Dr. Shapiro admitted, however, that it was difficult more generally to show a sustained aberrant response triggered by an initial cytokine upregulation (even if an unchecked wild infection *itself* might sustain an inflammatory response over time, independent of cytokines). Tr. at 142–43. And Melgaço mainly stood for the proposition that the Hep. A vaccine is effective in children—*not* that it can stimulate an autoimmune reaction. Melgaço at 3818-19.

More specifically, Dr. Shapiro endeavored to show that vaccination could specifically be associated with conditions comparable to FCA, although the evidence he could offer on this point was limited. The live attenuated Oka varicella vaccine ("Varivax"), for example, had been linked to vasculopathy and ischemic stroke. Shapiro First Rep. at 1; Shapiro Second Rep. at 3; A. Sabry et al., *Vaccine Strain Varicella-Zoster Virus-Induced Central Nervous System Vasculopathy as the Presenting Feature of DOCK8 Deficiency*, J. Allergy & Clinical Immunology 1225, 1227 (2014), filed as Ex. 23, Tab L on Oct. 5, 2021 (ECF No. 71-7) ("Sabry") (finding that varicella-zoster virus vasculopathy was caused by a vaccine strain, but acknowledging that the child in this case study was immunocompromised due to DOCK8 deficiency). However, because the Hepatitis A wild virus (unlike the varicella virus) has never been associated with FCA, the context in which a comparable vaccine could be linked to FCA is not present here.[13] Tr. at 43, 57–58, 123, 127, 143–44; Shapiro First Rep. at 2–3; Shapiro Second Rep. at 3.

Nevertheless, Dr. Shapiro argued, the Hep. A vaccine, and virus it contains, have been associated with *other* immune-mediated vascular phenomena that are analogous to FCA. Shapiro First Rep. at 2; Shapiro Second Rep. at 3. In particular, he referenced case reports involving the occurrence of Henoch-Schonlein Purpura ("HSP")[14] after a Hepatitis A infection.[15] Tr. at 57–62;

[13] In addition (and as Dr. Cummings later pointed out), the Sabry patient had an autosomal recessive DOCK8 mutation, which resulted in abnormal immune system function, further diminishing the value of any purported association with a varicella vaccine. Tr. at 184–84; Sabry at 1227.

[14] Dr. Shapiro described HSP as the most common vasculitis in children. It involves the small vessels, is seen in reaction to a variety of infections, and is believed to be the result of immune complex deposition. Tr. at 58.

[15] Dr. Shapiro maintained that literature specific to the wild Hepatitis A infection could still be relevant. Tr. at 59. The goal of vaccination is to produce an immune response that is directed against a particular viral antigen, and the Hep.

Shapiro First Rep. at 2; S. Altinkaynak et al., *Association of Henoch-Schonlein Purpura and Hepatitis A*, J. Emerging Med. 219, 219 (2006), filed as Ex. 17, Tab A on Oct. 5, 2021 (ECF No. 68-1) (case report involving 10-year-old boy experiencing immune complex mediated vasculitis with a Hep. A infection, although no determination was made as to when the infection might have begun); J. Chemli et al., *[Hepatitis A Infection and Henoch-Schonlein Purpura: A Rare Association]*, [Archives Pediatrics] 1202, 1202 (2004), filed as Ex. 17, Tab I on Oct. 5, 2021 (ECF No. 68-9)[16].

Other case reports were offered to establish a connection between Hepatitis A infection or vaccination and vasculitis. M. Dan & R. Yaniv, *Cholestatic Hepatitis, Cutaneous Vasculitis, And Vascular Deposits of Immunoglobulin M and Complement Associated with Hepatitis A Virus Infection*, Am. J. Med. 103, 104 (1990), filed as Ex. 23, Tab J on Oct. 5, 2021 (ECF No. 69-1) ("Dan & Yaniv") ("[t]he findings in our patient are the first direct evidence for the possible role of immune phenomena in the pathogenesis of hepatitis A-associated vasculitis in humans"); S. Jariwala et al., *Henoch-Schonlein Purpura After Hepatitis A Vaccination*, 107 Am. Coll. Allergy, Asthma & Immunology 180, 181 (2011), filed as Ex. 17, Tab M on Oct. 5, 2021 (ECF No. 69-3) ("Jariwala") (showing vaccine administration in the absence of other known risk factors for HSP were associated with the development of an immune complex mediated vasculitis; child received vaccine two weeks before onset, but also displayed associated rash within hours of vaccine). And a variety of cutaneous vasculitides,[17] including necrotizing vasculitis urticaria vasculitis, and cryoglobulinemic vasculitis,[18] were reported in the context of a Hepatitis A infection in children and adults. Tr. at 67–68; Shapiro First Rep. at 2. The vasculitides were generally thought to be mediated by immune complex deposition (which Dr. Shapiro had proposed might constitute the second "leg" of an aberrant immune response also resulting in FCA). Tr. at 62–66; Shapiro First Rep. at 2; Dan & Yaniv at 104; Jariwala at 181.

Next, Dr. Shapiro addressed the medical record, attempting to show how it supported his opinion. He began by proposing that B.P. had suffered from a right middle cerebral artery (MCA) infarction around August 25, 2015, directly attributable to FCA. Shapiro First Rep. at 1–2. This diagnosis was consistent with B.P.'s treating physicians at DHMC. Tr. at 13–15; Ex. 4 at 145; Shapiro First Rep. at 1. Ultimately, her stroke was caused by a) initial focal inflammation triggered

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A vaccine is specifically intended to provoke an immune response comparable to a wild infection. *Id*. at 59-60. Thus, evidence of an association with a wild infection could support the contention that the vaccine was also causal.

[16] Only the abstract of this article (which appears to have been written in French) was filed, so its contents cannot be verified.

[17] Leukocytoclastic vasculitis was also briefly discussed where activated white blood cells or neutrophils break down and release debris that lead to inflammation of small blood cells. Tr. at 67.

[18] Cryoglobulins are immunoglobulin M immune complexes which tend to aggregate under cold conditions and produce various side effects like vascular occlusion. Tr. at 66.

by the Hep. A vaccine, b) subsequent systemic inflammation leading to a transient hypercoagulable state, and c) a final spike in inflammation also attributable to the prior vaccine. Tr. at 44, 49–50, 113–14, 132–33, 139–40.

A number of record occurrences were deemed by Dr. Shapiro significant. For example, B.P. developed a rash 12 days after her October 2014 vaccinations, which Dr. Shapiro deemed a likely vaccine-associated form of cutaneous vasculitis. Shapiro First Rep. at 2; Ex. 4 at 67.[19] Shapiro First Rep. at 2. The record also, he noted, showed the existence of some kind of rash presentation in early September 2015. Ex. 4 at 163. While the treaters thought this was associated with medication B.P. was receiving to treat a possible varicella infection, Dr. Shapiro argued that it was possibly instead a manifestation of cutaneous vasculitis (although he ultimately downplayed the significance of this contention to his overall causation theory). Shapiro First Rep. at 2; Shapiro Second Rep. at 3.

After receipt of the second Hep. A dose in 2015, B.P. had documented (based on witness statements) symptoms of irritability and lethargy, which Dr. Shapiro opined was consistent with an acute vaccine reaction. Tr. at 48; Shapiro First Rep. at 2–3; Tr. at 179; Ex. 11 at 2. In addition, the record suggested that B.P. subsequently developed an infection and was treated with amoxicillin for acute otitis media. Shapiro First Rep. at 2; Ex. 4 at 29. Then, by the end of August 2015, B.P. showed signs of a cerebral injury attributable to a right basal ganglia ischemic stroke, which likely was triggered by an increase in her systemic inflammatory state due to the production of cytokines stimulated by the vaccination. Tr. at 48, 80; Shapiro First Rep. at 2. At bottom, he proposed, the inflammation encouraged by vaccination coupled with an infectious illness produced a blood clot leading to her stroke and permanent injury to the right basal ganglia. Tr. at 80.[20]

Another aspect of the medical record that Dr. Shapiro deemed significant were lab results from September 3, 2015, which established the presence of white blood cells in her CSF. Tr. at 88–89; Ex. 4 at 132. Dr. Shapiro proposed this to be evidence of an ongoing inflammatory process. Tr. at 44. 49–50, 113–14, 132–33, 139–40. At the same time, however, he disputed the contention of Respondent's expert that this supported the conclusion that there was a viral cause for B.P.'s stroke, maintaining that the white blood cell levels measured, while higher than normal (14 versus a normal range of 5 or less), were still too modest to be concerning. *Compare Id*. at 90, *with* Cummings First Rep. at 6–7. Typical cases of infectious meningitis could result in hundreds or thousands of white blood cells. Tr. at 90–93, 116–17.

[19] Dr. Shapiro conceded, however, that because there was no dermatologic examination or a biopsy, his contention as to the presence of vasculitis at this time was ultimately speculative (even if it remained plausible). Tr. 64–65, 129; Shapiro Second Rep. at 3.

[20] Dr. Shapiro also maintained that that B.P. could have been dehydrated, resulting in sluggish blood flow, since dehydration was a known clot formation risk. Tr. at 51, 133. The record, however, does not support the conclusion that B.P. was dehydrated at the time of her initial hospitalizations or symptoms onset.

Bulwarking Dr. Shapiro's opinion was the fact that he could not find anything else during the one to four weeks post-vaccination that could have triggered an immune-mediated process leading to FCA. Tr. at 44, 81. B.P.'s treaters had considered the possibility of some inflammatory trigger, such as infection. *Id.* at 84, 86–87; Ex. 4 at 144–45 (September 2, 2015 visit to Dr. Tadevosyan). To rule out other possible causes, B.P. underwent a fairly thorough workup[21] for almost all reported infectious causes of FCA, but did not identify anything specific. Tr. at 82, 89–90; Shapiro First Rep. at 2–3; Ex. 4 at 290–92. Her CSF was negative for enterovirus, cytomegalovirus, varicella-zoster virus, and other herpes viruses (Epstein-Barr virus and herpes simplex virus) by polymerase chain reaction and for Lyme by serology. Tr. at 82–83, 117–18; Shapiro First Rep. at 2; Ex. 4 at 290–92. They had also ruled out moyamoya disease or post-varicella arteriopathy. Tr. at 22, 25. And her treaters did not identify any genetic and epigenetic risk factors. Tr. at 43, 103.

Dr. Shapiro admitted, however, some limitations to his arguments about the lack of identified alternative causes. For example, none of B.P.'s treaters actually attributed her pediatric stroke to her Hep. A vaccine (beyond some uncorroborated speculation, or mere acknowledgement that the vaccination occurred before the stroke). Tr. at 124. There was also the fact that, as the record reveals, B.P. appears to have suffered from some kind of transient infection around August 25, 2015 (as evidenced at the time by fever and some vomiting)—almost immediately before the manifestation of her stroke symptoms. *Id.* at 87–90. He acknowledged this had occurred but argued that the symptoms she was reported to have experienced were not consistent with the type of infection that might cause neurologic symptoms. *Id*. at 87–88; Ex. 4 at 117. He also denied that the level of vascular inflammation seen in focal arteriopathy could occur within a day or two of a transient infection (although he offered nothing independent of his testimony to support his contention). *Id.* at 81, 130. At best, in Dr. Shapiro's view an infection would need to interact with some other underlying predisposition to stroke (but no such susceptibility has been demonstrated in this case). *Id.* at 36–39, 81-82; Shapiro Second Rep. at 1.

Besides offering his own opinion, Dr. Shapiro spent some time during his testimony attempting to rebut some of the arguments made by Respondent's expert, Dr. Dana Cummings. For example, he contested Dr. Cumming's assertion that B.P.'s stroke was possibly related to mild trauma. Tr. at 97–98. A hit to the head was, in his view, likely insufficient to produce tissue death unless it was a significant injury, which the record did not establish had occurred. *Id.*at 115–16.

He also disputed Dr. Cummings's argument that a viral illness might have the capacity to induce in a child "an unidentified hypercoagulability disorder or a transient hyper coagulable

[21] On cross examination, Dr. Shapiro explained that B.P. experienced the same type of testing in 2015 as what an average patient would experience today as the standard of care. Tr. at 110–12.

state," sufficient to lead to stroke.[22] Shapiro Second Rep. at 1–2; Tr. at 54-55. The workup B.P. received had not revealed that B.P. possessed any particular underlying susceptibility to hypercoagulability.[23] Even though literature[24] did suggest that minor infections could be associated with stroke risk generally, viral illnesses remained far more common in the pediatric population than stroke. Tr. at 33–34, 36–38, 134; Shapiro Second Rep. at 1; Cummings First Rep. at 7.[25] At most, it was possible that the seeming viral illness B.P. had experienced interacted with the Hep. A vaccine to create an overall, pro-inflammatory milieu in which stroke was more likely. Tr. at 45, 102–03, Tr. at 118–22, 135.

Finally, Dr. Shapiro turned to the issue of onset. The record, he maintained, establishes that B.P.'s onset likely began 11-12 days after receiving the Hep. A vaccine, and he deemed this a reasonable timeframe for stroke to occur due to an external trigger like infection or vaccination. Tr. at 105–06; Shapiro First Rep. at 2–3. The first Hep. A vaccine dose B.P. had received a year before had produced a robust immune response (although the record does not allow this conclusion), so any aberrant, pathogenic immune response to the second dose would likely occur in a shorter timeframe. Tr at 47–48. In particular, immune complex or antibody production peaks at one to four weeks following a second dose of Hep. A vaccine, while the production of inflammatory cytokines peaks at around ten days, so the date of B.P.'s stroke likely occurred at the peak of the inflammatory response to the vaccination. Tr. at 47–49; 74; 106.

To support this timeframe/onset conclusion, Dr. Shapiro offered several items of evidence. Post-varicella arteriopathy, for example, is seen by medical science as reasonably occurring any time within a *year* of a prior varicella infection. Shapiro First Rep. at 2; Braun at 545; Lanthier at 661–62. Other literature suggests that the median interval between infection and stroke is

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[22] A transient hypercoagulable state, defined by Dr. Shapiro, is a predisposition to clotting that is a response to an inciting factor like an infection; an underlying or chronic hypercoagulable state, by contrast, could be caused by a genetic or acquired factor. Tr. at 99–101.

[23] B.P. underwent an evaluation and it was eventually concluded that an additional workup of hereditary thrombophilia risk factors was not necessary, and therefore such disorders were not likely related to B.P.'s stroke. Tr. at 98–99; Shapiro First Rep. at 1–2; Ex. 4 at 210; 259; 291. Another common hypercoagulable disorder can be the product of an iron deficiency anemia. Tr. at 35, 99; Shapiro Second Rep. at 2; J. Maguire et al., *Association Between Iron-Deficiency Anemia and Stroke in Young Children*, Pediatrics 1053, 1053, 1055 (2007), filed as Ex. 23, Tab I on Oct. 5, 2021 (ECF No. 71-4). But this was also ruled out, as were other potential explanations for a systemic inflammatory disorders that could also provoke hypercoagulability. Tr. at 35; Shapiro Second Rep. at 2; Ex. 4 at 291, 297-98.

[24] *See* H. Fullerton, *The Vascular Effects of Infection in Pediatric Stroke (VIPS II) Study*, Nat'l Inst. Health 1, 1 (2017), filed as Ex. O on Jan. 25, 2018 (ECF No. 37-15). Dr. Shapiro acknowledged there is a certain age at which FCA becomes a more common presentation of stroke, but the pathogenic mechanisms of this are not yet understood. Tr. at 35.

[25] In so arguing, however, Dr. Shapiro did not outrightly disagree with the findings of one item of literature offered by Respondent and suggesting that infection probably leads to *more* strokes than vaccination (which in turn is likely protective against stroke). Tr. at 43, 119–22, 128–29; H. Fullerton et al., *Infection, Vaccination, and Childhood Arterial Ischemic Stroke: Results of the VIPS Study*, Neurology 1459, 1463 (2015), filed as Ex. G on Jan. 25, 2018 (ECF No. 37-7)

approximately four months, but stroke can still occur as early as one week after a documented infection, with the highest incidence of stroke occurring within two months. Shapiro First Rep. at 2; Amlie-Lefond II at 1562; E. Miravet et al., *Clinical and Radiological Features of Childhood Cerebral Infarction Following Varicella Zoster Virus Infection*, Developmental Med. & Child Neurology 417, 420–21 (2007), filed as Ex. 17, Tab U on Oct. 5, 2021 (ECF No. 70-1) ("Miravet") ("[d]ata from the current study and the literature review suggest that [post-varicella cerebral infarction] usually affects young, otherwise healthy children, commonly 3 to 4 months after chickenpox"); Jariwala at 181 (noting that the reported timeframe of HSP symptom onset was between 7 to 14 days after vaccination). For herpes zoster, risk of stroke is highest in the first one to four weeks after infection. S. Langan et al., *Risk of Stroke Following Herpes Zoster: A Self-Controlled Case-Series Study*, Clinical Infectious Diseases 1497, 1501 (2014), filed as Ex. 17, Tab O on Oct. 5, 2021 (ECF No. 69-5).

B. *Respondent's Experts – Dana D. Cummings, M.D., Ph.D.*

Dr. Cummings, a pediatric physician, testified on behalf of Respondent, and submitted two expert reports, in opposition to Petitioners' theory that the Hep. A vaccine had caused B.P.'s stroke. *See generally* Tr. at 145–205; Report, dated Jan. 24, 2018, filed as Ex. A (ECF No. 37-1) ("Cummings First Rep."); Report, dated Sept. 7, 2018, filed as Ex. Q (ECF No. 46-1) ("Cummings Second Rep.").

Dr. Cummings obtained his undergraduate degree from Brown University, doctorate from the University of Pennsylvania Institute of Neuroscience, and medical degree from the University of Pennsylvania School of Medicine. *See* Curriculum Vitae, filed as Ex. B (ECF No. 37-2) ("Cummings CV") at 1. He then completed his residency at the Children's Hospital of Philadelphia at the University of Pennsylvania and at Johns Hopkins University School of Medicine. Cummings CV at 1. Currently, he is an Associate Professor of Pediatrics, Division of Child neurology at the University of Pittsburgh, School of Medicine, Department of Pediatrics. *Id.* at 2; Tr. at 145. He is also the Director of the Pediatric Stroke Program for the Children's Hospital of Pittsburgh of UPMC, an Associate Director of the clinical research program, and a Director of the child neurology curriculum. Tr. at 145; Cummings CV at 2; Cummings First Rep. at 1. Additionally, he also serves as a site investigator of the National Institute of Health funded study on vascular effects of infection in pediatric strokes. Tr. at 148; Cummings First Rep. at 1. Overall, Dr. Cummings has approximately 300-400 pediatric stroke patients with about 60 percent of those patients having experienced an arterial ischemic stroke. Tr. at 11–12. He has published numerous articles on pediatric stroke symptoms and neurological issues. Tr. at 148; Cummings CV at 4–5. He is licensed to practice medicine, and is board certified in psychiatry and neurology. Tr. at 150; Cummings CV at 2–3; Cummings First Rep. at 1.

Dr. Cummings began with a discussion of the nature of FCA, and the different risk factors that can cause the blood flow disruption key to an arterial ischemic stroke. Tr. at 154. Two kinds

of arteriopathies are a focal arteriopathy (discussed in greater detail during Dr. Shapiro's testimony), or moyamoya disease, which Dr. Cummings defined as a progressive closing of the Circle of Willis in the brain. Tr. at 154. He also discussed arterial dissection, which is an abnormal tearing and separation of the layers of the arterial walls leading to obstruction of blood flow and resulting hemostasis and clot formation and propagation of clots. *Id.*; Cummings Rep. at 7. Dissections are most common in the extracranial internal carotid artery ("ICA") and vertebral arteries. Cummings Rep. at 7. However, dissections of the intracranial ICA and vertebral arteries can also occur, which can mimic FCA.[26] *Id.*; N. Dlamini et al., *Intracranial Dissection Mimicking Transient Cerebral Arteriopathy in Childhood Arterial Ischemic Stroke*, J. Child Neurology 1203, 1205 (2011), filed as Ex. D on Jan. 25, 2018 (ECF No. 37-4).

A cerebral vasculitis (where multiple vessels are affected) can also produce stroke, along with a varicella infection. Tr. at 152, 154–55. In addition, Dr. Cummings briefly touched on systemic disorders like sepsis, inflammation, or viral gastroenteritis. Tr. at 155. And although not discussed during his testimony, his reports mentioned mild trauma attributed to lenticulostriate vasculopathy as another possible cause, where there is typically a traumatic event that occurs a few minutes before the stroke symptoms appear. Cummings First Rep. at 7; E. Fidan et al., *A Case of Lenticulostriate Stroke Due to Minor Closed Head Injury in a 2-Year-Old Child: Role of Mineralizing Angiopathy.* Pediatric Emergency Care 1, 2 (2017), filed as Ex. F on Jan. 25, 2018 (ECF No. 37-6).

In Dr. Cummings's experience, it can be difficult to categorize an arterial ischemic stroke. Pediatric stroke also has a different group of risk factors than stroke in adults, because blood clotting and the coagulation system operate differently in young people (and are still subject to evolution as children age), while risk factors relevant to adults, like smoking, are not implicated. Tr. at 155–56; Cummings First Rep. at 5–6; A. Mallick et al., *Childhood Arterial Ischaemic Stroke Incidence, Presenting Features, and Risk Factors: A Prospective Population-Based Study*, Lancet Neurology 35, 42 (2014), filed as Ex. L on Jan. 25, 2018 (ECF No. 37-12) ("Mallick"). Pediatric arterial ischemic stroke is in fact uncommon. Cummings First Rep. at 5; L. Jordan & A. Hillis, *Challenges in the Diagnosis and Treatment of Pediatric Stroke,* Nature Rev.'s 199, 204 (2011), filed as Ex. J on Jan. 25, 2018 (ECF No. 37-10).

Because it is difficult to ascertain the pathophysiology of a pediatric stroke, risk factors that may contribute to its development can only be considered "putative." Tr. at 184; Cummings First Rep. at 6; Mallick at 42. In one study of 96 patients that suffered from a pediatric stroke, 17 percent of cases were considered idiopathic. Mallick at 42. In another study—a large, systematic review of arterial ischemic stroke risk factors in 676 children—the most commonly identified risk

[26] Early moyamoya disease can also have the appearance a focal arteriopathy, but B.P. never developed any evidence of severe stenosis of terminal ICA on MR angiography during the acute illness or on follow-up brain MRA. Cummings First Rep. at 7.

factors included arteriopathy (53 percent), cardiac disorders (31 percent), acute systemic conditions including fever greater than 48 hours and sepsis (22 percent), chronic systemic conditions (19 percent), and prothrombotic states (13 percent). Tr. at 185; Cummings First Rep. at 6; M. Mackay et al., *Arterial Ischemic Stroke Risk Factors: The International Pediatric Stroke Study*, 69 Annals Neurology 130, 132 (2011), filed as Ex. K on Jan. 25, 2018 (ECF No. 37-11) ("Mackay"). Children less than five years old represented 47 percent of the arterial ischemic stroke group. Tr. at 151; Mackay at 133.

Dr. Cummings agreed with Dr. Shapiro that the medical record supports the conclusion that B.P. experienced FCA associated with an arterial ischemic stroke. Tr. at 150–51. But he denied a cause could be identified. As in other pediatric stroke evaluations, there was no clear etiology for her stroke even after a thorough evaluation, leaving only a multifactorial explanation. *Id.* at 160, 191, 200; Cummings First Rep. at 6. However, Dr. Cummings deemed the most likely explanation was a viral illness, which in his view became a triggering factor for a stroke that manifested as an FCA variant. Tr. 151–52; Cummings First Rep. at 7. He argued it was also possible that "an unidentified hypercoagulability disorder or a transient hypercoagulable state" in the setting of viral infection could have been an additional factor. Tr. at 191; Cummings First Rep. at 7–8. In B.P.'s case, the arterial ischemic stroke appeared monophasic, without any significant progression of cerebrovascular disease beyond the acute phase, so it was appropriate to consider its cause as transient, whatever it was. Cummings First Rep. at 7.

To support this opinion, Dr. Cummings highlighted certain facts from the medical records. The day before stroke symptoms presented, B.P. had an elevated temperature and an episode of vomiting as part of a contagious illness that led to similar symptoms in her sibling.[27] Tr. at 163; Ex. 4 at 217–18; Cummings First Rep. at 7; Cummings Second Rep. at 2. Scientific studies have found that even a minor infection can increase the risk of stroke by 15-fold over the following three days. Tr. at 157; Cummings First Rep. at 7; N. Hills et al., *Timing and Number of Minor Infections as Risk Factors for Childhood Arterial Ischemic Stroke*, Neurology 890, 893 (2014), filed as Ex. H on Jan. 25, 2018 (ECF No. 37-8) ("Hills"). Using a multivariable analysis of minor infections prior to stroke in 102 cases of childhood arterial ischemic stroke and 306 age-matched controls), Hills observed a statistically reliable transient increased risk of stroke in the studied pediatric subjects who experienced a prior infection within as little as three days before the stroke's manifestation. Hills at 895. Hills's authors in fact opined that the specific nature of the infection

[27] There is some question as to the severity of the symptoms B.P. experienced on August 25th, which Dr. Cummings characterized as mild to moderate. Tr. at 194. He cited to a noted from Dr. Rutman from August 29, 2015, which stated that B.P. stayed home on August 26th but was no longer ill. Tr. at 194–97; Ex. 4 at 111–12; Cummings Second Rep. at 2. B.P.'s parents denied other symptoms of fever, chills, headache, stiff neck, nausea, vomiting, abnormal gait, mental status changes, or rashes. Tr. at 197; Ex. 4 at 111. Although this note suggested to Petitioners that B.P. was no longer ill by the evening of August 25th, Dr. Cummings argued that the note was not entirely clear as to when B.P.'s symptoms resolved.

itself mattered less than the *fact* of a prior infection (since it was likely that the "infectious/inflammatory state" itself that was the instigating factor). *Id.*

Another item of literature—the largest prospective study of risk factors of pediatric stroke—concluded that there was a significant increase risk of stroke when there was an infection in the prior week (although risk was lesser if the infection preceded stroke by a month).[28] Tr. at 158–60; Cummings First Rep. at 7; H. Fullerton et al., *Infection, Vaccination, and Childhood Arterial Ischemic Stroke: Results of the VIPS Study*, Neurology 1459, 1463 (2015), filed as Ex. G on Jan. 25, 2018 (ECF No. 37-7) ("Fullerton"). Fullerton also looked at the effects of vaccination, but the authors did not find an increased risk of stroke after vaccination. Tr. at 159–60; Fullerton at 1464–465. In fact, the data observed in Fullerton suggested that vaccination in the prior week actually *reduced* the risk of having a stroke. Tr. at 159; Fullerton at 1462.

Another significant factor, in Dr. Cummings's view, better supporting infection as causal was the finding of 14 white blood cells in B.P.'s cerebrospinal fluid. Ex. 4 at 131–32; Cummings First Rep. at 6–7; Cummings Second Rep. at 1. He noted that five or more white blood cells in a two-year-old is usually considered a sign for meningitis or possibly encephalitis,[29] which is why B.P.'s physician proposed treatments specific for these illnesses. Tr. at 162, 187–88; Ex. 4 at 218; Cummings Second Rep. at 1; E.J. Piña-Garza et al., *Chapter 2: Altered States of Consciousness*, Fenichel's Clinical Pediatric Neurology 47, 54–55 (2013), filed as Ex. V on Sept. 7, 2018 (ECF No. 46-6) (diagnostic threshold for meningitis in children was five or more white blood cells in the CSF).

This CSF finding also suggested that cardio-embolic stroke or stroke due to craniocerebral dissection or other forms of trauma were less likely. Tr. at 198; Cummings Second Rep. at 6–7; E. Riou et al., *Cerebrospinal Fluid Analysis in The Diagnosis and Treatment of Arterial Ischemic Stroke*, Pediatric Neurology 1, 5 (2008), filed as Ex. M on Jan. 25, 2018 (ECF No. 37-13) (emphasizing the diagnostic significance of CFS testing in treatment of pediatric stroke). Even though, as Dr. Shapiro maintained, spinal fluid can show a white blood cell increase with a stroke simply because of brain injury, an increase of white blood cells for this reason would typically be accompanied by whole hemisphere trauma, plus more white blood cells than the volume B.P.'s testing revealed. Tr. at 90, 198. It was thus more likely that the elevated white blood cell count was related to an infectious process than secondary to the brain being injured from the stroke. *Id.* B.P.'s treaters (Drs. Mott, Morse, and Lukovits) all seemed more concerned that B.P. had experienced some kind of viral or parainfectious process. Tr. at 193; Ex. 4 at 168, 185; Ex. 21 at

[28] The study, however, found that although a preceding infection increased the risk by 6-fold, a viral infection alone cannot fully explain why a child has an ischemic stroke and there is typically a preceding event. Tr. at 189–90; Cummings First Rep. at 7.

[29] Even though B.P. eventually tested negative for HSV, this did not in Dr. Cumming's view eliminate the suspicion of encephalitis completely. Tr. at 188.

10; Cummings Second Rep. at 1. Dr. Cummings admitted, however, that B.P.'s lab work revealed no other abnormalities directly establishing an infectious disease as causal. Tr. at 198–99; Cummings Second Rep. at 6–7.

Another potential explanatory factor Dr. Cummings observed in the medical record was the fact that B.P. had suffered from a mild head injury after she hit her head on a table three weeks before her stroke. Ex. 4 at 211. This could be enough to have caused a dissection. Tr. at 160. However, Dr. Cummings admitted that the presence of white blood cells in CSF testing, plus the lack of red blood cells in the cerebrospinal fluid, were inconsistent with an arterial dissection. Tr. at 160–61.

The Hep. A vaccine, by contrast, was unlikely to have caused B.P.'s stroke. Tr. at 164. From a record standpoint, Dr. Cummings noted, there was no evidence that B.P.'s post-vaccination reaction reflected anything out of the ordinary, beyond the usual malaise well-associated with vaccines. *Id.* at 179; Ex. 11 at 2. And none of B.P.'s providers proposed any role for the vaccine (while actively exploring the possibility of an infectious cause).[30] Tr. at 164. Admittedly, testing had never confirmed a specific infection, but Dr. Cummings noted that such tests could not always identify a specific virus. *Id.* at 165. Research, however, continued to identify new viral causes for pediatric stroke. *Id.* at 165, 167. For the vaccine to be causal, Dr. Cummings indicated, he would need (at a minimum) some evidence that the wild Hep. A infection can impact the blood vessels of a pediatric brain—but not only was there no such reliable scientific proof here, but also no evidence that this had happened to B.P. (other than her admitted stroke). *Id.* at 200.

Dr. Cummings questioned the persuasiveness and reliability of Dr. Shapiro's theory that the Hep. A vaccine provoked an immune complex and transient hypercoagulable state sufficient to result in FCA. Tr. at 151, 191; Cummings Second Rep. at 7. First, he noted that infections inherently impacted individuals differently from vaccines, with the latter almost always being less severe in the immune system response they elicited. Tr. at 168, 182. Second, there was reliable evidence that certain infections can trigger strokes, but not much suggesting the same was true with respect to the Hep. A wild infection (other than regarding distinguishable conditions). Thus, there were no cases of FCA or a large vessel stroke of the middle cerebral artery or internal carotid artery where a Hep. A infection preceded the event. Tr. at 171–72. At most, a form of vasculitis had been so associated, but it affects the skin and kidneys, and has never been linked to any form of cerebral arteriopathy or cerebral vasculitis. *Id.* at 172.

[30] At most, during B.P.'s hospitalization some treaters discussed a post-vaccination phenomenon, but Dr. Cummings argued that their focus remained on a post-infectious etiology. Tr. at 191–93. For example, at an appointment with pediatrician Dr. Shessler on September 11, 2015, the exact etiology of B.P.'s stroke was deemed to remain unknown, but a viral etiology remained as a likely cause. Ex. 4 at 593.

More significantly, Dr. Cummings maintained, there is no comparable evidence that *any* vaccines can trigger strokes.[31] On the contrary, medical literature actually establishes that vaccines are *protective* against stroke. Tr. at 168–71; Fullerton at 1463; J. Donahue et al., *Varicella Vaccination and Ischemic Stroke in Children: Is There an Association?,* Pediatrics e228, e232 (2009), filed as Ex. E on Jan. 25, 2018 (ECF No. 37-5) ("Donahue") (finding no relationship between varicella vaccination and risk of stroke, and that "[m]ultivariable models revealed strong associations between ischemic stroke and established risk factors but no increase in the risk of ischemic stroke at any time in the 12 months after varicella vaccination"). As Donahue revealed, the relationship was lacking even when there was a wild virus association. Thus, reliable science did not support the conclusion that the Hep. A vaccine represented an essential trigger capable of provoking a pediatric stroke.[32] Tr. at 181. Indeed, in Dr. Cummings's view even a minor infection had a greater capacity to cause stroke than a robust immune response stimulated by a vaccine. Tr. at 181.

Besides the above, Dr. Cummings questioned whether several items of literature offered by Petitioners or Dr. Shapiro actually supported their causation theory. Batista-Duharte, for example, focused solely on possible mechanisms attributable to vaccine *adjuvants*, with no data regarding the Hep. A vaccine, and there was no mention of hypercoagulable state or stroke among the adverse effects associated with adjuvants. Cummings Second Rep. at 3; Batista-Duharte at 101. Kashiwagi described no data on cytokine responses to the Hep. A vaccine. Cummings Second Rep. at 3; Kashiwagi at 680. And since no adverse effect of the Hep. A vaccine was described in Melgaço, its findings as well were not ultimately helpful to Petitioners. Cummings Second Rep. at 3.

On the topic of timing, Dr. Cummings agreed that B.P.'s stroke occurred one day after her viral illness—but twelve days after vaccination. Tr. at 173. He deemed the likely first symptoms of B.P.'s arterial ischemic stroke as her abnormal arm movements noted by her grandmother on August 26, 2015. *Id.* at 153; Ex. 4 at 104; Cummings First Rep. at 6; Cummings Second Rep. at 2. There was some subsequent fluctuation in symptoms that likely represented onset of a hemiparesis as well as a component of increased tone and possible movement disorder related to arterial ischemic stroke in the right caudate and putamen. Cummings First Rep. at 1; Ex. 4 at 691. But such symptoms were consistent with the conclusion that stroke's risk increased close-in-time to a viral illness. Tr. at 173; Hills at 890 ("[m]inor infections appear to have a strong but short-lived effect on pediatric stroke risk, while cumulative burden of infection had no effect"). The Fullerton study also found the highest risk of stroke occurred in the week after illness (while deeming vaccination protective). Tr. at 173; Fullerton at 1463. Thus, the timing of B.P.'s onset was more

[31] At most, Dr. Cummings noted, some scientific evidence supports the conclusion that the Hep. A vaccine is associated with meningitis or encephalitis occasionally, but less so with vasculitis. Tr. at 169.

[32] Dr. Cummings stated that certain factors needed to occur to support such a theory—primarily, it needed a patient who had a genetic immune system disorder like DOCK8 syndrome. Tr. at 202.

consistent with the close-in-time infection as having been causal, rather than the more distant vaccination almost two weeks before.

III. Procedural History

As noted above, the case was initiated in 2016 and was for some time presided over by a different special master. ECF No. 1. By January 2017, Petitioners had filed all relevant medical records, affidavits, and a Statement of Completion. ECF No. 13. Respondent filed a Rule 4(c) report on April 6, 2017, contesting Petitioners' right to compensation. ECF No. 18. Petitioners then filed their expert report from Dr. Kevin A. Shapiro on September 25, 2017, with Respondent thereafter filing an expert report from Dr. Dana D. Cummings on January 25, 2018. ECF Nos. 27, 37. Petitioners then filed a supplemental expert report on May 24, 2018, with Respondent thereafter filing a supplemental expert report on September 7, 2018. ECF Nos. 41, 46. After the matter was transferred to me in March 2021, I held a status conference with the parties and subsequently set the matter for a hearing, to be held from November 2-3, 2021. ECF No. 59. The trial occurred as scheduled and lasted only one day, November 2, 2021, and the parties submitted post hearing briefs on February 27, 2022, and March 14, 2022, respectively. ECF Nos. 78, 80. The matter is now ripe for resolution.

IV. Applicable Legal Standards

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

To receive compensation in the Vaccine Program, a petitioner must prove either: (1) that he suffered a "Table Injury"—i.e., an injury falling within the Vaccine Injury Table—corresponding to one of the vaccinations in question within a statutorily prescribed period of time or, in the alternative, (2) that his illnesses were actually caused by a vaccine (a "Non-Table Injury"). *See* Sections 13(a)(1)(A), 11(c)(1), and 14(a), as amended by 42 C.F.R. § 100.3; § 11(c)(1)(C)(ii)(I); *see also Moberly v. Sec'y of Health & Hum. Servs.*, 592 F.3d 1315, 1321 (Fed. Cir. 2010); *Capizzano v. Sec'y of Health & Hum. Servs.*, 440 F.3d 1317, 1320 (Fed. Cir. 2006).[33] In this case, Petitioners do not assert a Table claim.

For both Table and Non-Table claims, Vaccine Program petitioners bear a "preponderance of the evidence" burden of proof. Section 13(1)(a). That is, a petitioner must offer evidence that

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

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

In attempting to establish entitlement to a Vaccine Program award of compensation for a Non-Table claim, a petitioner must satisfy all three of the elements established by the Federal Circuit in *Althen*, 418 F.3d at 1278: "(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."

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

Petitioners may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu v. Sec'y of Health & Hum. Servs.*, 569 F.3d 1367, 1378–79 (Fed. Cir. 2009) (citing *Capizzano*, 440 F.3d at 1325–26). Special masters, despite their expertise, are not empowered by statute to conclusively resolve what are essentially thorny scientific and medical questions, and thus scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Id.* at 1380. Accordingly, special masters must take care not to increase the burden placed on petitioners in offering a scientific theory linking vaccine to injury. *Contreras*, 121 Fed. Cl. at 245.

In discussing the evidentiary standard applicable to the first *Althen* prong, the Federal Circuit has consistently rejected the contention that it can be satisfied merely by establishing the

proposed causal theory's scientific or medical *plausibility*. *See Boatmon v. Sec'y of Health & Hum. Servs.*, 941 F.3d 1351, 1359 (Fed. Cir. 2019); *see also LaLonde v. Sec'y of Health & Hum. Servs.*, 746 F.3d 1334, 1339 (Fed. Cir. 2014) ("[h]owever, in the past we have made clear that simply identifying a 'plausible' theory of causation is insufficient for a petitioner to meet her burden of proof" (citing *Moberly*, 592 F.3d at 1322)). And petitioners always have the ultimate burden of establishing their *overall* Vaccine Act claim with preponderant evidence. *W.C. v. Sec'y of Health & Hum. Servs.*, 704 F.3d 1352, 1356 (Fed. Cir. 2013) (citations omitted); *Tarsell v. United States*, 133 Fed. Cl. 782, 793 (2017) (noting that *Moberly* "addresses the petitioner's overall burden of proving causation-in-fact under the Vaccine Act" by a preponderance standard).

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

Medical records and statements of a treating physician, however, do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. Section 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder v. Sec'y of Health & Hum. Servs.*, 88 Fed. Cl. 706, 746 n.67 (2009) ("there is nothing . . . that mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted"). As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should be weighed against other, contrary evidence also present in the record—including conflicting opinions among such individuals. *Hibbard v. Sec'y of Health & Hum. Servs.*, 100 Fed. Cl. 742, 749 (2011) (not arbitrary or capricious for special master to weigh competing treating physicians' conclusions against each other), *aff'd*, 698 F.3d 1355 (Fed. Cir. 2012); *Veryzer v. Sec'y of Dept. of Health & Hum. Servs.*, No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), *mot. for review denied*, 100 Fed. Cl. 344, 356 (2011), *aff'd without opinion*, 475 F. Appx. 765 (Fed. Cir. 2012).

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the

phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Hum. Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must align with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id.* at 1352; *Shapiro v. Sec'y of Health & Hum. Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. denied after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 503 F. Appx. 952 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Hum. Servs.*, No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for rev. denied* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

B. *Legal Standards Governing Factual Determinations*

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

As noted by the Federal Circuit, "[m]edical records, in general, warrant consideration as trustworthy evidence." *Cucuras*, 993 F.2d at 1528; *Doe/70 v. Sec'y of Health & Hum. Servs.*, 95 Fed. Cl. 598, 608 (2010) ("[g]iven the inconsistencies between petitioner's testimony and his contemporaneous medical records, the special master's decision to rely on petitioner's medical records was rational and consistent with applicable law"), *aff'd*, *Rickett v. Sec'y of Health & Hum. Servs*., 468 F. App'x 952 (Fed. Cir. 2011) (non-precedential opinion). A series of linked propositions explains why such records deserve some weight: (i) sick people visit medical professionals; (ii) sick people attempt to honestly report their health problems to those professionals; and (iii) medical professionals record what they are told or observe when examining their patients in as accurate a manner as possible, so that they are aware of enough relevant facts to make appropriate treatment decisions. *Sanchez v. Sec'y of Health & Hum. Servs.*, No. 11–685V, 2013 WL 1880825, at *2 (Fed. Cl. Spec. Mstr. Apr. 10, 2013); *Cucuras v. Sec'y of Health & Hum. Servs.*, 26 Cl. Ct. 537, 543 (1992), *aff'd*, 993 F.2d at 1525 (Fed. Cir. 1993) ("[i]t strains reason to

conclude that petitioners would fail to accurately report the onset of their daughter's symptoms").

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

However, the Federal Circuit has also noted that there is no formal "presumption" that records are accurate or superior on their face to other forms of evidence. *Kirby v. Sec'y of Health & Hum. Servs.*, 997 F.3d 1378, 1383 (Fed. Cir. 2021). There are certainly situations in which compelling oral or written testimony (provided in the form of an affidavit or declaration) may be more persuasive than written records, such as where records are deemed to be incomplete or inaccurate. *Campbell v. Sec'y of Health & Hum. Servs*., 69 Fed. Cl. 775, 779 (2006) ("like any norm based upon common sense and experience, this rule should not be treated as an absolute and must yield where the factual predicates for its application are weak or lacking"); *Lowrie*, 2005 WL 6117475, at *19 ("[w]ritten records which are, themselves, inconsistent, should be accorded less deference than those which are internally consistent") (quoting *Murphy*, 23 Cl. Ct. at 733)). Ultimately, a determination regarding a witness's credibility is needed when determining the weight that such testimony should be afforded. *Andreu*, 569 F.3d at 1379; *Bradley v. Sec'y of Health & Hum. Servs*., 991 F.2d 1570, 1575 (Fed. Cir. 1993).

When witness testimony is offered to overcome the presumption of accuracy afforded to contemporaneous medical records, such testimony must be "consistent, clear, cogent, and compelling." *Sanchez*, 2013 WL 1880825, at *3 (citing *Blutstein v. Sec'y of Health & Hum. Servs*., No. 90–2808V, 1998 WL 408611, at *5 (Fed. Cl. Spec. Mstr. June 30, 1998)). In determining the accuracy and completeness of medical records, the Court of Federal Claims has listed four possible explanations for inconsistencies between contemporaneously created medical records and later testimony: (1) a person's failure to recount to the medical professional everything that happened during the relevant time period; (2) the medical professional's failure to document everything reported to her or him; (3) a person's faulty recollection of the events when presenting testimony; or (4) a person's purposeful recounting of symptoms that did not exist. *La Londe v. Sec'y of Health & Hum. Servs*., 110 Fed. Cl. 184, 203–04 (2013), *aff'd*, 746 F.3d 1334 (Fed. Cir. 2014). In making a determination regarding whether to afford greater weight to contemporaneous medical records or other evidence, such as testimony at hearing, there must be evidence that this decision was the

result of a rational determination. *Burns*, 3 F.3d at 417.

C. *Analysis of Expert Testimony*

Establishing a sound and reliable medical theory often requires a petitioner to present expert testimony in support of his claim. *Lampe v. Sec'y of Health & Hum. Servs*., 219 F.3d 1357, 1361 (Fed. Cir. 2000). Vaccine Program expert testimony is usually evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594–96 (1993). *See Cedillo v. Sec'y of Health & Hum. Servs.*, 617 F.3d 1328, 1339 (Fed. Cir. 2010) (citing *Terran v. Sec'y of Health & Hum. Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999). Under *Daubert*, the factors for analyzing the reliability of testimony are:

> (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community.

Terran, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592–95).

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

Respondent frequently offers one or more experts in order to rebut a petitioner's case. Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Hum. Servs*., 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d at 1362). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743

(quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 146 (1997)); *see also Isaac v. Sec'y of Health & Hum. Servs*., No. 08–601V, 2012 WL 3609993, at *17 (Fed. Cl. Spec. Mstr. July 30, 2012), *mot. for review den'd*, 108 Fed. Cl. 743 (2013), *aff'd*, 540 F. App'x. 999 (Fed. Cir. 2013) (citing *Cedillo*, 617 F.3d at 1339). Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Moberly*, 592 F.3d at 1325–26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Hum. Servs*., 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

D. *Consideration of Medical Literature*

Both parties filed numerous items of medical and scientific literature in this case, but not all such items factor into the outcome of this decision. While I have reviewed all the medical literature submitted in this case, I discuss only those articles that are most relevant to my determination and/or are central to Petitioners' case—just as I have not exhaustively discussed every individual medical record filed. *Moriarty v. Sec'y of Health & Hum. Servs.*, No. 2015–5072, 2016 WL 1358616, at *5 (Fed. Cir. Apr. 6, 2016) ("[w]e generally presume that a special master considered the relevant record evidence even though he does not explicitly reference such evidence in his decision") (citation omitted); *see also Paterek v. Sec'y of Health & Hum. Servs.,* 527 F. App'x 875, 884 (Fed. Cir. 2013) ("[f]inding certain information not relevant does not lead to—and likely undermines—the conclusion that it was not considered").

ANALYSIS

I. Pediatric Arterial Ischemic Stroke and its Treatment in Vaccine Program Decisions

As the experts agreed, FCA involves the narrowing of the distal branches of the internal carotid artery, which supplies blood to a large part of the brain. The resulting limited blood flow predisposes the individual to the formation of a clot, which can in turn provoke a stroke. There are several risk factors associated with the development of a pediatric stroke, and overall it is difficult to identify its pathophysiology. Some factors include arteriopathy, cardiac disorders, acute systemic conditions like prolonged fever and sepsis, chronic systemic conditions, and prothrombotic states. Mackay at 132. Even after extensive workups, the causes may be idiopathic. Mallick at 42. In this case, both parties accept that FCA directly caused B.P.'s pediatric arterial ischemic stroke—they only disagree as to whether the Hep. A vaccine could have initially triggered the FCA.

I have identified one prior case where a Program petitioner argued that the Hep. A vaccine (in combination with the pneumococcal conjugate and varicella vaccines) caused a minor child to suffer from a stroke (and seizure). *Martz v. Sec'y of Health & Hum. Servs.*, No. 12-329V, 2013 WL 4477865, at *1 (Fed. Cl. Spec. Mstr. July 29, 2013). But the matter was settled without the decision of a special master, and thus provides no insight into factors bearing on causation herein.[34]

Otherwise, there a number of cases in which adults alleged a stroke to be vaccine-caused. Reasoned decisions in those matters did not result in favorable entitlement determinations. *See e.g., Hayward v. Sec'y of Health & Hum. Servs.*, No. 15-005V, 2018 WL 2772495, at *17 (Fed. Cl. Spec. Mstr. May 4, 2018) ("[t]he problem with this evidence is that it does not go far enough, leaving unlinked propositions in the overall causation 'chain', or overstating the findings for an otherwise-reliable item of medical/scientific literature"); *Flores v. Sec'y of Health & Human Servs.*, No. 10–489V, 2013 WL 5587390 (Fed. Cl. Spec. Mstr. Sept. 12, 2013) (denying entitlement for a spinal cord infarction following the HPV vaccine because Petitioner did not have the "critical" genetic criteria to meet the causation theory), *mot. for rev. den'd*, 115 Fed. Cl. 157 (2014), *aff'd*, 586 F. Appx. 588 (Fed. Cir. 2014); *Carrino v. Sec'y of Health & Human Servs.*, No. 08–266V, 2013 WL 3328903 (Fed. Cl. Spec. Mstr. June 6, 2013) (denying entitlement because petitioner had not set forth a reliable theory to causally connect the flu vaccine to lateral medullary syndrome); *Francis v. Sec'y of Health & Human Servs.*, No. 99–286V, 2000 WL 1517676 (Fed. Cl. Spec. Mstr. Aug. 31, 2000) (finding that petitioner had not met his burden in establishing that an encephalopathy occurred following the DTP vaccination administration precipitating a stroke); *Wilson v. Sec'y of Health & Human Servs.*, No. 90–795V, 1992 WL 118955 (Cl. Ct. May 15, 1992) (determining that there was not preponderant evidence that petitioner suffered an encephalopathy followed by a stroke and a brain injury after receiving the DTP vaccine). None of these cases provided a similar theory to that alleged here, however.

[34] Decisions from different cases do not control the outcome herein, with only Federal Circuit decisions setting legal standards to which new claims must adhere. *Boatmon*, 941 F.3d at 1358–59; *Hanlon v. Sec'y of Health & Hum. Servs*., 40 Fed. Cl. 625, 630 (1998). Nevertheless, special masters reasonably draw upon their experience in resolving Vaccine Act claims. *Doe v. Sec'y of Health & Hum. Servs*., 76 Fed. Cl. 328, 338–39 (2007) ("[o]ne reason that proceedings are more expeditious in the hands of special masters is that the special masters have the expertise and experience to know the type of information that is most probative of a claim") (emphasis added). They would thus be remiss in ignoring prior cases presenting similar theories or factual circumstances, along with the reasoning employed in reaching such decisions.

II. Petitioners Have Not Carried Their Burden of Proof[35]

A. *Althen Prong Two*

Even if a reliable causation theory associating the Hep. A vaccine to pediatric stroke had been offered (and as discussed below, I do not find that to be the case), the record does not permit the conclusion that the Hep. A vaccine likely "did cause" B.P. to experience a pediatric stroke.

Most significantly, no treaters thought so—and it appears from this record that B.P. received excellent care from a number of competent professionals. Although there was speculation when B.P. began her treatment that the Hep. A vaccine might have been causal, none of the treaters ultimately connected her illness to it. And given a somewhat lengthy course, there were many opportunities to refine the diagnostic explanation for her condition. Otherwise, the record only reveals a temporal association[36] between B.P.'s receipt of the Hep. A vaccine on August 14, 2015, and subsequent onset, proposed around 11-12 days after vaccination.

The record evidence of what occurred *between* vaccination and B.P.'s symptoms also does not suggest the vaccine was causal, since other than some vaccination-related malaise (alleged in Petitioners' witness statements) nothing from the record establishes a reaction.[37] There is simply no evidence (other than the transitory malaise) to which Petitioners can point that would suggest that in the almost two-week period before onset, anything approaching what Dr. Shapiro's theory delineated (an aberrant immune response) was occurring. *K.L. v. Sec'y of Health & Hum. Servs.*, No. 12-312V, 2017 WL 1713110, at *15 (Fed. Cl. Spec. Mstr. Mar. 17, 2017) (noting no evidence of some immune process between vaccination and onset of petitioner's symptoms), *mot. for review den'd,* 134 Fed. Cl. 579 (2017).

By contrast, the record more firmly establishes a different factor that could have caused B.P.'s stroke. In particular, B.P. likely suffered from a contagious, inflammatory illness merely two days before her stroke. Ample literature substantiates that, all things being equal, even a minor infection is more likely causal of stroke than a vaccination. *See* Fullerton at 1462; Hills at 890.

[35] I address the *Althen* prongs herein in order of their significance to my Decision, rather than in the order they are typically presented.

[36] Petitioners have placed too much weight on the temporal association, but this type of temporal association alone cannot establish such a causal relationship. *Moberly*, 592 F.3d at 1323 ("a proximate temporal association alone does not suffice to show a causal link between the vaccination and the injury.") (quoting *Grant*, 956 F.2d at 1148); *de Bazan*, 539 F.3d at 1352 ("the proximate temporal relationship prong requires preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact."); *Pafford*, 451 F.3d at 1358 (finding that the Special Master properly required evidence of a temporal relationship between the vaccine and petitioner's injury).

[37] I do not credit Dr. Shapiro's speculation that B.P. experienced some kind of vasculitis after her receipt of the first vaccine dose a year prior, thus suggesting the possibility of a second reaction the following year.

Additionally, B.P. had 14 white blood cells in her cerebrospinal fluid—a result strongly supportive of the possibility of an existing infectious process at work. Though Dr. Shapiro persuasively noted that viral illnesses in children are more common than strokes as a general matter, this does not negate the literature associating mild infection with stroke—even within a few days. Hills at 893; Fullerton at 1462.

Dr. Shapiro was not able to downplay the role of B.P.'s illness immediately prior to his stroke. While the infection B.P. seems to have experienced was transient and thus self-limiting, this does not diminish its potential association with stroke. The same transient reaction to the Hep. A. vaccine is supported by the record, but without a close-in-time comparable reaction before the infection. Dr. Shapiro also admitted that it could be difficult in many cases to even identify a prior infectious cause. Shapiro First Rep. at 1. This is the case even though many *other* viral infections have been more positively associated with FCA than the Hep. A infection.

I acknowledge that this record does not allow me to conclude in any preponderant sense what other factors *could* be more likely causal than the vaccine—and thus I make no finding as to what preponderantly *did* likely cause her stroke. It is unquestionably true that no other causal infection was identified, even after substantial testing (although the ruling out of a possible cause does not inherently render vaccination more likely). *K.L.*, 2017 WL 1713110, at *16. And while Dr. Cummings made some good points about the meaningfulness of the CSF testing results as underscoring the likelihood of an infectious process as causal, they do not inerrantly support his opinion. But entitlement claims can fail simply because an alternative cause is not proven, since petitioners have the initial burden to preponderantly demonstrate the *vaccine* was most likely causal. That has not been done here.

B. *Althen Prong One*

Petitioners have also not preponderantly established a reliable theory of causation that the Hep. A vaccine "can cause" a pediatric stroke. Dr. Shapiro proposed that a) focal inflammation attributable to the innate response to the Hep. A vaccination could result in b) systemic inflammatory condition that raised the general probability of forming a clot (a transient hypercoagulable state), and then c) another spike in inflammation associated with an antecedent infection, leading to infarction that (like other forms of vascular injury) could be attributable to immune complex deposition associated with the inflammation.

Dr. Shapiro was unquestionably a knowledgeable, qualified expert with demonstrated understanding of the injury at issue and its context. He also offered a number of individual items of reliable medical and scientific literature to support his opinion. It certainly is the case that many other infectious viruses are associated with injuries comparable to FCA, like cutaneous vasculitis, and a handful of case reports delineate circumstances in which a child experienced a vascular

injury (such as HSP or vasculitis) after vaccinations, including the Hep. A vaccine. I also do not contest the fact (as set forth in articles like Kashiwagi) that vaccines generally stimulate cytokine upregulation, that reliable science shows the Hep. A vaccine invokes a reasonably robust immune response sufficient to make it protective, or that some combination of innate and adaptive immune responses could play a role in an FCA leading to stroke. Moreover, the idea that immune complex deposition is part of the pathogenesis of FCA after *some* different causal environmental factors, or that this kind of immune "step" is critical to certain classes of vasculitides, was also reasonably advanced.

But on the critical issue of vaccine causation relevant to the Hep. A vaccine—a topic which did raise questions of immunology, which somewhat exceeded his otherwise-proven medical expertise—Dr. Shapiro could not marshal sufficient reliable evidence (either based on his own work or contained in independent studies or articles) to reliably establish that the Hep. A vaccine can trigger a pediatric stroke via FCA, and several weeks after the vaccine's administration. Dr. Shapiro's demonstrated competence as an expert in the relevant illness was not enough to imbue his causation theory on the immunologic impact of vaccination with the needed reliability.

A particular hurdle (which Dr. Shapiro acknowledged several times) was the lack of recognition from the scientific community that vaccines are a risk factor for FCA. Indeed, the contrary is the case—vaccines are deemed likely *preventative* of stroke, whereas minor infections have a greater capacity to cause stroke. Donahue at e232. Also significant, as Dr. Shapiro admitted, is the fact that even an underlying Hep. A infection is not associated with arterial ischemic strokes—whereas a number of other wild infectious viruses, such as varicella, are. Shapiro First Rep. at 2–3; Shapiro Second Rep. at 3. And even where a particular viral infection is so associated, its vaccine counterpart is not always similarly associated. *See* Donahue at e232.

The actual mechanism proposed herein was also speculative (at least when applied to FCA, as opposed to other kinds of comparable but distinguishable injuries, like HSP) and not reliably bulwarked with other scientific evidence, as pointed out by Dr. Cummings. For example, Dr. Shapiro cited to Kao, Ribai, Tsai, and Leeuwis as studies suggesting an immune mechanism was the primary cause of stroke, but the authors concluded in each that a direct infection beforehand was essential to trigger the initial immune response. Tr. at 174; Cummings First Rep. at 10. And these items of literature all involved different infections in any event. In addition, the immunologic impact of wild infection versus vaccination cannot be conflated, merely because both implicate the immune system comparably—the scale of impact is demonstrably different (and with vaccines this is by design). Fullerton at 1462.

Additionally, Dr. Shapiro argued that both the innate immune response and the adaptive immune response were at play, but the process he outlined was ultimately too speculative, or tried to connect disparate (if reliable) evidentiary items in an unpersuasive manner. Thus, the

combination of a heightened coagulable state with subsequent immune complex deposition may well explain *other* kinds of arteriopathies (such as HSP) that have been linked to a Hep. A infection (at least in case reports—a type of evidence usually given little weight in Program cases).[38] But it has not reliably shown that FCA *itself* would also so unfold, especially since FCA has not been established to be associated with immune complex deposition in the first place. The capacity of the Hep. A vaccine to generally be immunogenic is also not particularly probative evidence of the same vaccine's capacity to cause a pathologic response. Fullerton at 1462. And the character of the "handoff" in immune response in this context leading to pathology, from the cytokine upregulation referenced by Dr. Shapiro[39] to the adaptive response that would occur thereafter, remains opaquely demonstrated. The pathologic process he has described may be reasonably plausible, but it has not reliably been shown to *likely* occur after receipt of the Hep. A vaccine.

Otherwise, Petitioners' causation theory overall relies on a chain of propositions that are limited in scope and only circumstantially support their argument. Of course, the Program permits claimants to offer *any* kind of evidence that supports a petition, and petitioners can in many cases prevail because of indirect proof. But here, Petitioners' arguments about the capacity of the Hep. A vaccine to cause FCA are rebutted by *direct* proof offered by Respondent showing not only that even mild infectious processes are more likely causal, but also that vaccination has been shown to be *protective* against stroke (by eliminating the possibility of the infectious cause in the first place). The Hep. A vaccine has not been preponderantly shown to have the capacity to cause FCA.[40]

C. *Althen Prong Three*

The experts did not disagree on the most likely date for onset of B.P.'s stroke, with Drs. Shapiro and Cummings favoring an 11–12-day post-vaccination onset. Petitioners stated that during that timeframe, B.P. had issues with her motor functions, specifically that she "didn't want to use her left arm," was "holding her cup different," and "kept her hand in a fist." Ex. 4 at 662.

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[38] It is recognized that case reports provide lukewarm evidentiary support for causation. *See Campbell*, 97 Fed. Cl. at 668 ("[c]ase reports do not purport to establish causation definitively, and this deficiency does indeed reduce their evidentiary value ... [but] the fact that case reports can by their nature only present indicia of causation does not deprive them of all evidentiary weight.").

[39] I note as well that in prior cases in which petitioners relied on articles like Kashiwagi, I have rejected the contention that even reliable scientific studies showing that vaccines do induce cytokine production do not in turn amount to a preponderant showing that this upregulation either (a) lasts long enough to spur along a pathologic process, or (b) is sufficient in magnitude to be likely disease-causing. *Dean on behalf of I.D. v. Sec'y of Health & Hum. Servs.*, No. 13-808V, 2017 WL 2926605, at *17 (Fed. Cl. June 9, 2017).

[40] In what is sometimes referred to as a "*Shyface*" claim, petitioners sometimes maintain that a vaccine could be a substantial factor in causing an injury even if other factors also played an important role, such that one cannot be deemed predominant over any other. *Shyface*, 165 F.3d at 1352. But Respondent has not conceded herein any vaccine association, and I do not otherwise find that one exists, whereas the causal association with infection has been preponderantly established. I thus do not find that the vaccine was any kind of factor in causing FCA.

Additionally, during this time she had a temperature and an episode of vomiting. *Id.*; Ex. 11 at 2. This corroborates the conclusion that B.P.'s symptoms occurred no later than August 26.

There are some deficiencies with such an onset under Dr. Shapiro's theory. For example, he proposes a cytokine upregulation process that would last most of the 12 days before onset, even though (as I have found in other cases) this increase is usually transient in the absence of an ongoing, unchecked infection. *Bender v. Sec'y of Health & Hum. Servs.*, No. 11-693V, 2018 WL 3679637, at *27 (Fed. Cl. Spec. Mstr. July 2, 2018). By contrast, he downplayed a post-infectious onset of a day or two (as would be the case here if B.P.'s illness was explanatory), even though Respondent's literature, like Hills, was supportive of infection-caused stroke occurring within three days. Dr. Shapiro otherwise relied on literature which described symptoms of *infection* and ischemia-related symptoms (*see e.g.*, Amlie-Lefond II at 1562; Miravet at 420–21; Jariwala at 181), even though vaccination is somewhat distinguishable.

Nevertheless, the timing of onset of B.P.'s stroke symptoms is consistent with Petitioners' causation theory for how long the aberrant process would take and has some reliable support. Had the theory *itself* been preponderantly established, this finding would be assistive to Petitioners. But because I have found that the Hep. A vaccine has not been shown to cause FCA, or that it did in this case, the fact that onset was consistent with an unsuccessful causation theory does not aid the claim.

CONCLUSION

The Pelletiers have my utmost sympathy for the suffering they have experienced, and I credit their demonstrated efforts to ameliorate B.P.'s condition and provide loving care for her. It is clear from this record that, based on temporal association alone, they reasonably believed the Hep. A vaccine might have triggered her stroke. But the record evidence does not permit me to conclude that the vaccine can likely cause stroke—meaning the temporal association with injury is only that.

A Program entitlement award is only appropriate for claims supported by preponderant evidence. Here, Petitioners have not made such as showing. Petitioners are therefore not entitled to compensation.

In the absence of a motion for review filed pursuant to RCFC Appendix B, the Clerk of the Court **SHALL ENTER JUDGMENT** in accordance with the terms of this decision.[41]

IT IS SO ORDERED.

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

[41] Pursuant to Vaccine Rule 11(a), the parties may expedite entry of judgment if (jointly or separately) they file notices renouncing their right to seek review.