

In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Case No. 11-508V

Filed: September 5, 2013

PUBLISHED

CLIFTON HAIGLER and *
CHARITY HAIGLER, legal representatives *
of a minor child, THOMAS THURLOW *
HAIGLER, *

Special Master Dorsey

Petitioners, *

v. *

Entitlement; Varivax; varicella
vaccine; encephalitis;
encephalopathy

SECRETARY OF HEALTH *
AND HUMAN SERVICES, *

Respondent. *

Peter J. Sarda, Creech Law Firm, Raleigh, NC, for petitioners.

Claudia B. Gangi, U.S. Department of Justice, Washington, DC, for respondent.

RULING ON ENTITLEMENT¹

I. Introduction

On August 9, 2011, Clifton and Charity Haigler (“petitioners”) filed a petition for compensation under the National Vaccine Injury Compensation program (“the Program”)², as the legal representatives of their son, Thomas Thurlow Haigler (“Thomas”), in which they alleged that a varicella vaccination that Thomas received on October 2, 2008, caused him to suffer

¹ Because this published ruling contains a reasoned explanation for the action in this case, the undersigned intends to post this decision on the website of the United States Court of Federal Claims, in accordance with the E-Government Act of 2002 § 205, 44 U.S.C. § 3501 (2006). In accordance with the Vaccine Rules, each party has 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). Further, consistent with the rule requirement, a motion for redaction must include a proposed redacted ruling. If, upon review, the undersigned agrees that the identified material fits within the requirements of that provision, such material will be deleted from public access.

² The Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, 42 U.S.C. §§ 300aa-10 et seq. Hereafter, individual section references will be to 42 U.S.C. § 300aa.

encephalitis. Petition (“Pet.”) at 4 ¶¶18, 20.³ Petitioners further alleged that the vaccination “caused permanent brain damage and will continue to block [Thomas’s] mental development.” Id. at 4, ¶18. Petitioners subsequently described Thomas’s injury as an encephalopathy. See Joint Stipulation (“Jnt. Stip.”) filed Apr. 1, 2013, at 2. Respondent recommended against compensation, stating that petitioners have not presented adequate evidence to show that Thomas’s varicella vaccination caused him to suffer an encephalopathy. See id.; see also Respondent’s Rule 4 Report (“Resp’t’s Report”) at 9.

The parties filed expert reports in support of their respective positions. Petitioners filed three reports⁴ from neurologist Dr. Jean-Ronel Corbier, one of Thomas’s treating physicians. Pet’rs’ Ex. 11 at 34-37; Pet’rs’ Ex. 18; Pet’rs’ Ex. 20. Respondent filed a report from neurologist Dr. Gregory L. Holmes. Resp’t’s Ex. A. Both parties also filed prehearing submissions outlining their respective positions. Pet’rs’ Prehearing Submission, filed Apr. 1, 2013; Resp’t’s Prehearing Submission, filed Apr. 22, 2013.

The parties participated in mediation with another special master, but could not resolve this matter informally. Thus, an entitlement hearing was held on May 9, 2013, in Washington, DC, during which petitioners and the parties’ respective experts testified. Neither the parties nor the undersigned requested post-hearing submissions. This matter is now ripe for adjudication.

Respondent does not dispute that Thomas suffered from encephalitis and respondent’s expert agrees that Thomas’s tests were consistent with an encephalopathy. Jnt. Stip. at 1, ¶3; Resp’t’s Ex. A at 6. The sole issue to be decided, therefore, is whether “Thomas suffered an encephalopathy as the direct and proximate result of the varicella vaccine administered on October 2, 2008.” Jnt. Stip. at 2. Petitioners have provided circumstantial evidence demonstrating that Thomas’s subject vaccination more likely than not caused his injuries, which satisfies their burden under Althen v. Sec’y of Health & Human Servs., 418 F.3d 1274, 1280 (Fed. Cir. 2005). See Capizzano v. Sec’y of Health & Human Servs., 440 F.3d 1317, 1324 (Fed. Cir. 2006) (circumstantial evidence may satisfy a petitioner’s burden of proof). Therefore, the undersigned finds that a preponderance of the evidence supports a finding that Thomas suffered encephalitis and an encephalopathy as a result of his receipt of a varicella vaccination on October 2, 2008.

II. Factual Background

Thomas was born on September 18, 2006, in Stanly County, North Carolina. Pet’rs’ Ex. 1 at 1. Thomas was born at 38 weeks gestation, Pet’rs’ Ex. 2 at 7, and he weighed 5 pounds, 12 ounces, and was 18.5 inches long. Pet’rs’ Ex. 3 at 11. There were no observed physical abnormalities. Id. Thomas’s Apgar scores were 8 and 9, at 1 and 5 minutes, respectively. Id. The results of the North Carolina State newborn screening blood tests were normal. Pet’rs’ Ex. 8 at 209.

³ All references to petitioners’ filings refer to the pagination as set forth by petitioners in their exhibits, and not the PDF page numbers referenced on CM/ECF.

⁴ One of these reports was a letter Dr. Corbier wrote on January 6, 2011, during his treatment of Thomas. See Pet’rs’ Exhibit 11 at 34-37.

Over the next year, Thomas had a number of childhood illnesses, but was otherwise considered “normal,” Pet’rs’ Ex. 7 at 1, “alert [and] active,” and “well developed.” Pet’rs’ Ex. 8 at 19. At his 10 and 12 month well-child visits, Thomas’s developmental milestones were assessed by use of the “Ages & Stages Questionnaires”⁵ (“ASQ”). Thomas’s communication, gross and fine motor skills, problem solving and personal social skills were noted to be normal. Pet’rs’ Ex. 8 at 65, 71. Thomas’s hearing and vision were also noted to be normal. Id.

On November 13, 2007, Thomas presented to his pediatrician with complaints of “tugging” his ears, nasal draining, and a cough. The assessment was bilateral otitis media,⁶ resolving. Id. at 74. At this visit, Thomas received a number of vaccinations including the mumps-measles-rubella (“MMR”) and Varivax vaccines.⁷ Pet’rs’ Ex. 5 at 2. At his 18 month check-up, on April 24, 2008, Thomas’s physical exam was normal except for slight edema of his nose. Pet’rs’ Ex. 8 at 200. Thomas was noted to be healthy, and his 18 month ASQ reflected normal development. Id. at 201.

On October 2, 2008, Thomas, age two, received a second full dose of the Varivax vaccine at the Stanly County Health Department.⁸ Pet’rs’ Ex. 5 at 2. Approximately two weeks later, on October 16, 2008, Thomas was brought to his pediatrician by his mother, with complaints of fever, cough, runny nose, mouth lesions and mouth pain, decreased appetite, and an episode of shaking for approximately 10 minutes. Pet’rs’ Ex. 8 at 75. While in the pediatrician’s office, Thomas began having tonic/clonic seizures. Initially, his temperature was 100.9°F axillary, but it increased to 104.4°F. Id. at 76. Diastat and acetaminophen were administered to Thomas. Id. Thomas continued having seizures and EMS was called. Id.

Thomas was taken from the pediatrician’s office by ambulance to the Stanly Regional Emergency Department. Pet’rs’ Ex. 9 at 2. On arrival at 1:39 P.M., Thomas was having a seizure and was unresponsive. Id. at 3. At 1:46 P.M., Thomas was noted to be listless, post-ictal and unresponsive. Id. At 3:39 P.M., he was in severe respiratory distress with rhonchi and wheezing. Id. at 6. Thomas was intubated. Id. at 3. Thomas was diagnosed as having status epilepticus, seizure disorder, fever, bacteremia, and pneumonitis. Id. at 7-8.

At approximately 3:45 P.M., Thomas was taken by air transport from the Stanly Regional Emergency Room to the Carolinas Medical Center Pediatric Intensive Care Unit (“PICU”).

⁵ Ages & Stages Questionnaires, Second Edition, Bricker et al., 1999 Paul H. Brookes Publishing Co.

⁶ Otitis media is “inflammation of the middle ear.” Dorland’s Illustrated Medical Dictionary (32d ed. 2012) at 1451 (“Dorland’s”).

⁷ Thomas also received vaccinations for hepatitis A and haemophilus influenza type B. Pet’rs’ Ex. 5 at 1-2.

⁸ Thomas received this second dose in error. Pet’rs’ Ex. 11 at 34; see also Tr. 19. Based on Thomas’s medical history, Dr. Corbier opines that Thomas accidentally received this second dose because the administering health care provider was unaware that Thomas had already received his first dose. Tr. 19. The parties dispute whether this second dose was administered at an appropriate time frame, see Tr. 19-20, 102, but that issue is not necessary to resolve the dispositive question in this case of whether Thomas’s second varicella vaccine caused his injuries.

Upon arrival, while being transferred to the crib in the PICU, Thomas was inadvertently extubated. Pet'rs' Ex. 10 at 266-67. Supplemental oxygen was administered and Thomas's oxygen saturation remained at 100%. Id. at 267. He remained stable after extubation. Id. at 229.

On his first night in the PICU, October 16, 2008, Thomas had questionable seizure activity of symmetric, rhythmic jerking of his legs and smacking of his lips. Id. at 232. An electroencephalogram ("EEG") was conducted on October 17, 2008, and revealed right frontal epileptiform activity. Id. at 256. An MRI of the brain was normal. Id. Results from the cerebrospinal fluid analysis ("CSF")⁹ conducted on October 16, 2008, showed 63 white blood cells ("WBCs") with 63% lymphocytes, 25% segmented neutrophils ("segs") and 5% monocytes ("monos"). Id. at 258; 945. There were 702 red blood cells ("RBCs") and Thomas's protein level was 17. Id. at 258. The laboratory studies were significant for elevated liver function levels, and a diagnosis of hepatitis was made. Id. at 258-59.

On October 16, 2008, an initial assessment performed in the PICU revealed that Thomas had multiple ulcers on his lips with dried blood. Id. at 269. These were also described as "several labial [mouth] ulcers." Id. at 229. On October 18, 2008, Dr. Ahmed documented two lesions on Thomas's lips and three "crusted vesicular lesions." Id. at 917. On October 19, 2008, the medical records state that Thomas's lip lesions and left auricle (ear) blisters had resolved. Id. at 214. In the neurologist's progress note dated October 21, 2008, an erythematous skin rash was documented. The neurologist noted, "Question whether drug eruption or part of underlying possible infectious process." Id. at 203.

From October 17 to 18, 2008, Thomas's neurological examinations were abnormal, and he was unresponsive. On October 18, 2008, Dr. Amina Ahmed diagnosed Thomas with meningoencephalitis¹⁰ and hepatitis. Pet'rs' Ex. 10 at 251. Tests for herpes simplex virus ("HSV"), enterovirus, Rocky Mountain Spotted Fever, Bartonella, cytomegalovirus, Toxoplasma, Epstein-Barr Virus ("EBV"), lymphocytic choriomeningitis virus ("LCMV") (mouse exposure), and Arbovirus were negative. Id. at 239-47, 255, 908. Additionally, bacterial and viral cultures of Thomas's blood, urine and stool were negative. Id. There is no documentation which establishes that any of the health care providers who were treating Thomas at the time were aware that he had received the varicella vaccine two weeks prior.

⁹ "Cerebrospinal fluid (CSF) analysis is a laboratory test to examine a sample of the fluid surrounding the brain and spinal cord. This fluid is a clear, watery liquid that protects the central nervous system from injury and cushions it from the surrounding bone structure. It contains a variety of substances, particularly glucose (sugar), protein, and white blood cells from the immune system." [http://medical-dictionary.thefreedictionary.com/Cerebrospinal+Fluid+\(CSF\)+Analysis](http://medical-dictionary.thefreedictionary.com/Cerebrospinal+Fluid+(CSF)+Analysis). The reference ranges for normal results are: WBC (0-5), RBC (0), monos (14-45), segs (0-6%), and lymphocytes (40-80%). Pet'rs' Ex. 10 at 945. The reference range for normal results for protein are 15-45 mg/de CSF. Mosby's Manual of Diagnostic and Laboratory Tests 632 (4th ed. 2012).

¹⁰ Meningoencephalitis is "inflammation of the brain and meninges." Dorland's at 1133. The meninges are "the three membranes that envelop the brain and spinal cord." Id. at 1132.

On October 19, 2008, Thomas's CSF results were WBC 4, RBC 850, and protein 22. Pet'rs' Ex. 10 at 945. The CSF cultures were negative for bacteria. Id. at 918. Results for the HSV and enterovirus tests by polymerase chain reaction ("PCR") test of the CSF were negative. Id. at 936-39.

On October 19, 2008, Thomas again experienced jerking of his legs and smacking of his lips. Id. at 232. A CT scan of his brain showed diffuse cerebral edema with loss of gray-white matter differentiation. Id. at 210. A video EEG showed suppression consistent with diffuse encephalopathy of a nonspecific nature. Id. at 527. On October 21, 2008, Thomas's cough and gag reflexes were absent. Id. at 232. A repeat CT scan showed progressive loss of gray-white matter differentiation. Id. at 210. An MRI performed on October 21, 2008, revealed global edema. Id. While in the PICU, Thomas experienced episodes of teeth grinding, moaning, posturing and hypertonicity. He was intubated from October 21 to 24, 2008, due to a decline in his neurological status. Id. at 196, 183. An EEG performed on October 22, 2008, showed diffuse disorganization, suppression and slow brain waves, but no epileptic activity. Id. at 998.

On October 28, 2008, Thomas was diagnosed with meningoencephalitis of unclear etiology. Pet'rs' Ex. 10 at 160. On October 31, 2008, the PICU attending physician diagnosed Thomas with an altered mental status secondary to a "viral meningoencephalitis." Id. at 148. On November 2, 2008, Thomas was noted to be "neurologically devastated, likely secondary to viral meningoencephalitis." Id. at 138.

Thomas was discharged from the Carolinas Medical Center on November 5, 2008. His discharge diagnoses included meningoencephalitis, new onset of seizures, and hepatitis. Pet'rs' Ex. 10 at 13. Thomas was transferred to a rehabilitation facility for physical therapy, occupational and speech therapy. Pet'rs' Ex. 10(b) at 1078.

On April 17, 2009, Ms. Haigler called Thomas's pediatrician Dr. Linda Lawrence to report that Thomas had received a vaccine on October 2, 2008, and then had "an episode" on October 16, 2008, where he "broke out in blisters around his mouth and ears." Pet'rs' Ex. 8 at 305. Ms. Haigler asked if the varicella vaccine could have caused her son's encephalitis. Id. She further stated that "her family physician¹¹ told her that the varicella vaccine probably could have caused encephalitis." Id. Dr. Lawrence reviewed Thomas's vaccine history, and noted that the vaccine given to him on October 2, 2008, was not his first varicella vaccine. Id. Dr. Lawrence, or someone in her office, documented that the "medical opinion was that vaccine did not cause encephalitis."¹² Id.

¹¹ The "family physician" is not identified.

¹² Although it is not clear, the undersigned assumes the statement that the "vaccine did not cause [Thomas's] encephalitis" is attributable to Dr. Lawrence, and has given the statement careful consideration. Neither the unidentified family physician nor Dr. Lawrence prepared a written report or testified at the hearing, and they did not set forth any explanation for the basis of the opinions that Thomas's subject vaccine did or did not cause his encephalitis. Moreover, neither respondent nor her expert Dr. Holmes discussed either the family physician's or Dr. Lawrence's opinion at the hearing, and Dr. Holmes did not discuss this in his report. Thus, it is difficult to assess the basis for these statements in the record.

Petitioners subsequently sought a second opinion regarding the cause of and treatment for Thomas's seizures. Pet'rs' Ex. 11 at 1-4. On April 23, 2009, Thomas was seen by Dr. Jean-Ronel Corbier, a neurologist, at his Northeast Pediatric Neurology office. Id. at 1. Dr. Corbier diagnosed Thomas with encephalitis, encephalopathy and partial complex seizures. Id. at 3. Dr. Corbier subsequently reviewed Thomas's medical records and ordered and reviewed his diagnostic studies. Id. at 4.

On September 28, 2009, Dr. Corbier noted that a brain MRI performed on Thomas on August 21, 2009, showed global atrophy, and that an EEG performed on the same day showed "diffuse epileptiform discharges and slowing" compatibility with a "diffuse underlying encephalopathy." Id. at 9. On November 9, 2009, Dr. Corbier interpreted a 24-hour video EEG performed of Thomas as showing "frequent, multifocal and generalized epileptiform discharges that at times were almost continuous." Id. at 75. A single-photon emission computed tomography ("SPECT") scan performed on November 9, 2007, showed decreased brain perfusion. Id. at 14. In February 2010, Thomas was diagnosed with cortical blindness. Pet'rs' Ex. 8 at 126.

On February 16, 2011, at Dr. Corbier's request, Thomas was seen by Dr. David Rugar, a pediatric infectious disease specialist, for a consultation regarding whether it was safe for Thomas to receive the diphtheria-tetanus-acellular-pertussis ("DTaP") vaccine. Pet'rs' Ex. 10(c) at 2674-76. Based on his examination of Thomas and his review of Thomas's records and medical history, Dr. Rugar wrote a letter to Dr. Corbier in which he opined that Thomas should receive a DTaP vaccine. Id. at 2676. Dr. Rugar also explained:

My impression is this is a boy who had encephalitis of unknown origin. I see no reason to assume that it was related to his second VZ vaccine as there is no evidence for this and this would certainly be an unusual reaction. Encephalitis can occur with varicella zoster vaccine, but it is usually not that severe and should not occur with his second shot preferentially.

Id. at 2675.

Based on the most recent medical records from 2010, Thomas continues to have seizures, has a gastrostomy tube (also called a G-tube)¹³ for nutrition, has limited motor function, and is non-verbal. Id. at 2016, 2039-40.

On April 1, 2013, the parties filed a joint stipulation of undisputed facts. Among other things, "[t]he parties agree that Thomas received his first varicella vaccine on November 13, 2007, and a second dose . . . on October 2, 2008." Jnt. Stip. at 1. They also agree that "Thomas suffered from encephalitis and that his parents first sought medical treatment for this condition on October 16, 2008." Id.

¹³ A gastrostomy feeding tube insertion is the placement of a feeding tube through the skin and the stomach wall, directly into the stomach. See Dorland's at 766.

Varicella, commonly known as chickenpox, is a member of the herpes virus family, and is caused by the varicella zoster virus (“VZV”). Pet’rs’ Ex. 19 at 1;¹⁴ Resp’t’s Ex. D at 3.¹⁵ Potential complications of a VZV infection include neurologic complications, including encephalitis and meningitis. Resp’t’s Ex. D at 3-4. “In 1995, the live, attenuated virus vaccine, Varivax . . . was licensed in the United States.” *Id.* at 6. Prior to the use of the vaccine, however, chickenpox was a common childhood illness. *Id.* at 4. Secondary infections, including central nervous system (“CNS”) complications, such as encephalitis, were a common cause of hospitalization and even death. *Id.* at 5. Vaccination against the VZV has been very effective in reducing the complications of a varicella infection, and the vaccine has an excellent safety profile. Pet’rs’ Ex. 38 at 1-2.¹⁶

III. Discussion

The Vaccine Act established the Program to compensate vaccine-related injuries and deaths. 42 U.S.C. § 300aa-10(a). “Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award ‘vaccine-injured persons quickly, easily, and with certainty and generosity.’” *Rooks v. Sec’y of Health & Human Servs.*, 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908 at 3, reprinted in 1986 U.S.C.C.A.N. at 6287, 6344).

A. Standards for Adjudication

Petitioners’ burden of proof is a preponderance of the evidence. 42 U.S.C. § 300aa-13(a)(1). The preponderance of the evidence standard, in turn, has been interpreted to mean that a fact is more likely than not. *Moberly v. Sec’y of Health & Human Servs.*, 592 F.3d 1315, 1322 n. 2 (Fed. Cir. 2010). Proof of medical certainty is not required. *Bunting v. Sec’y of Health & Human Servs.*, 931 F.2d 867, 873 (Fed. Cir. 1991). A petitioner who satisfies this burden is entitled to compensation unless the government can prove, by a preponderance of the evidence that the vaccinee’s injury is “due to factors unrelated to the administration of the vaccine.” §300aa-13(a)(1)(B).

B. Elements of petitioners’ claim

When a petitioner alleges that an injury listed on the Vaccine Injury Table (“the Table”) occurs within the time frame set forth in the Table, then petitioner’s vaccine claim is deemed a Table claim, and a presumption of vaccine causation attaches. *See* § 300aa-14; *see also* 42 C.F.R. § 100.3. If, however, a petitioner alleges an injury that is not listed on the Table (such as

¹⁴ Sujit Iyer et al., “Herpes Zoster and Meningitis Resulting from Reactivation of Varicella Vaccine Virus in an Immunocompetent Child,” 53:6 *Annals of Emergency Med.* 792, 792 (2009).

¹⁵ Institute of Medicine (“IOM”), *Adverse Effects of Vaccines: Evidence and Causality* 239 (Kathleen Stratton et al. eds., 2012).

¹⁶ Giorgos Chouliaras et al., *Vaccine-Associated Herpes Zoster Ophthalmicus and Encephalitis in an immunocompetent Child*, 125:4 *Pediatrics* 969 (2010).

the injury alleged in this case), the vaccine claim is deemed a non-Table case, and there is no presumption of causation. Rather, petitioner must satisfy his burden of proof. See § 300aa-13(a)(1)(A).

To receive compensation under the Program, petitioners must prove either: (1) that Thomas suffered a “Table Injury”—i.e., an injury listed on the Vaccine Injury Table—corresponding to a vaccine that he received, or (2) that Thomas suffered an injury that was actually caused by the varicella vaccine. See 42 U.S.C. §§ 300aa-13(a)(1)(A) and 11(c)(1); Capizzano, 440 F.3d at 1319-20. Petitioners must show that the vaccine was “not only a but-for cause of the injury but also a substantial factor in bringing about the injury.” Moberly v. Sec’y of Health & Human Servs., 592 F.3d 1315, 1321 (Fed. Cir. 2010) (quoting Shyface v. Sec’y of Health & Human Servs., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)).

Because petitioners do not allege Thomas suffered a Table injury, they must prove that the varicella vaccine Thomas received caused his injury. To do so, they must establish, by preponderant evidence: (1) a medical theory causally connecting the vaccine and Thomas’s injury (“Althen Prong One”); (2) a logical sequence of cause and effect showing that the vaccine was the reason for his injury (“Althen Prong Two”); and (3) a showing of a proximate temporal relationship between the vaccine and his injury (“Althen Prong Three”). Althen, 418 F.3d at 1278; 42 U.S.C. § 300aa–13(a)(1) (requiring proof by a preponderance of the evidence).

Because the causation theory must relate to the injury alleged, a petitioner must provide a reputable medical or scientific explanation that pertains specifically to the vaccinee’s case, although the explanation need only be “legally probable, not medically or scientifically certain.” Knudsen v. Sec’y of Health & Human Servs., 35 F.3d 543, 548-49 (Fed. Cir. 1994). Petitioners cannot establish entitlement to compensation based solely on their assertions. Rather, a vaccine claim award must be supported either by medical records or by the opinion of a competent physician. § 300aa-13(a)(1). In determining whether petitioners are entitled to compensation, the special master shall consider all material contained in the record, § 300aa-13(b)(1), including “any . . . conclusion, [or] medical judgment . . . which is contained in the record regarding . . . causation . . . of the petitioner’s illness.” §300aa-13(b)(1)(A). Thus, the undersigned must weigh the submitted evidence and the testimony of the parties’ offered experts and rule in petitioners’ favor when the evidence weighs in their favor. Moberly, 592 F.3d at 1325-26 (“Finders of fact are entitled—indeed, expected—to make determinations as to the reliability of the evidence presented to them and, if appropriate, as to the credibility of the persons presenting that evidence”); Althen, 418 F.3d at 1280-81.

i. Althen Prong One: Petitioners’ Medical Theory

Under Althen Prong One, petitioners must set forth a medical theory explaining how the received vaccine could have caused the sustained injury. Andreu v. Sec’y of Health & Human Servs., 569 F.3d 1367, 1375 (Fed. Cir. 2009). Under this prong, petitioners must make a showing that the received vaccine “can” cause the alleged injury. Pafford v. Sec’y of Health & Human Servs., 451 F.3d 1352, 1355-56 (Fed. Cir. 2006).

Petitioners’ theory of causation need not be medically or scientifically certain, Knudsen, 35 F.3d at 548-49, but it must be informed by “sound and reliable medical or scientific

explanation.” Id. at 548; see also Veryzer v. Sec’y of Health & Human Servs., 98 Fed. Cl. 214, 223 (2011) (noting that special masters are bound by both § 300aa-13(b)(1) and Vaccine Rule 8(b)(1) to consider only evidence that is both “relevant” and “reliable”). If petitioners rely upon a medical opinion to support their theory, the basis for the opinion and the reliability of that basis must be considered in the determination of how much weight to afford the offered opinion. See Broekelschen v. Sec’y of Health & Human Servs., 618 F. 3d 1339, 1347 (Fed. Cir. 2010) (“The special master’s decision often times is based on the credibility of the experts and the relative persuasiveness of their competing theories.”); Perreira v. Sec’y of Health & Human Servs., 33 F.3d 1375, 1377 n.6 (Fed. Cir. 1994) (“An expert opinion is no better than the soundness of the reasons supporting it”) (citing Fehrs v. United States, 620 F.2d 255, 265 (Ct. Cl. 1980)).

a. Petitioners’ Expert, Dr. Corbier

Dr. Corbier became Thomas’s treating pediatric neurologist in April of 2009. Pet’rs’ Ex. 18 at 1. Dr. Corbier’s medical background includes a three-year fellowship in pediatric neurology at the Children’s Hospital Medical Center in Cincinnati, Ohio, from 1997 to 2000. Pet’rs’ Ex. 30 at 4 (Dr. Corbier’s curriculum vitae). Dr. Corbier has been board-certified in neurology with a special qualification in child neurology since 2002, and he has had a full-time clinical pediatric neurology practice for approximately 12 years. Id. at 5; Tr. 5-6. Dr. Corbier was awarded the North Carolina Patient Choice Award in 2008, 2009, 2010, and 2011. Pet’rs’ Ex. 30 at 5.

Dr. Corbier opined that Thomas’s October 2, 2008 varicella vaccination caused him to develop meningoencephalitis,¹⁷ which resulted in prolonged seizures, Pet’rs’ Ex. 20 at 4, “global developmental delay, hypoxic ischemic encephalopathy, and very refractory epilepsy.” Tr. 8; see also Pet’rs’ Ex. 20 at 4; Pet’rs’ Ex. 18 at 1. Dr. Corbier considers all of these injuries to be part of a more generalized seizure disorder. See Pet’rs’ Ex. 20 at 3. Dr. Corbier describes Thomas’s current condition as “a severe, ongoing seizure disorder . . . along with severe neurological regression . . . which persists till this day.” Id. at 1.

Dr. Corbier posited three mechanisms for the development of seizures post-vaccination. Id. at 1-2. “The first involves an autoimmune response in which brain cells come under attack (‘neuroimmune’) by the body’s own antibodies.” Id. “The second is a direct infection¹⁸ of the brain or meningoencephalitis from a vaccination where a live strain (‘live attenuated’) vaccine, such as varicella . . . is used.” Id. at 2. The third mechanism is “reactivation of a previous infection.” Id.

During the hearing, Dr. Corbier described his proposed mechanisms as “good models” of scientific explanations to explain how Thomas’s complication could occur. Tr. 12. Dr. Corbier

¹⁷ Dr. Corbier described meningoencephalitis as “inflammation of the covering of the brain [which is] called the meninges and of the brain itself.” Tr. 9. Encephalitis is “inflammation of the brain,” and it has many types with a wide variety of symptom manifestation. Dorland’s at 612. Dr. Corbier explained that the inflammation “can present or be accompanied by various neurological problems, including epilepsy.” Tr. 9.

¹⁸ The parties used the terms “direct infection” and “primary infection” interchangeably. See, e.g., Tr. 44, 91.

was unable to identify which of the above mechanisms caused Thomas's seizure disorder due to lack of specific testing information. Tr. 24, 57-58.

Dr. Corbier testified as follows:

While the research has shown that while rare, it's not a common occurrence at all, but while rare, in certain cases vaccination, including in kids with varicella, can lead to devastating neurological complications, including meningoencephalitis . . . So based on all of this information, my conclusion has been and still continues to be that the varicella vaccine much more likely than not contributed to Thomas Haigler's devastating change as far as meningoencephalitis, hypoxic ischemic encephalopathy, and the devastation that we see today.

Tr. 11.

(1) Autoimmune Response Theory

Dr. Corbier's first proposed theory of causation, an "autoimmune response" theory of causation, is unclear. Dr. Corbier did not expound on this theory in either his reports or during his testimony at the hearing. See Pet'rs' Ex. 20 at 2-3. He stated the mechanism could cause a "post-infectious process where the immune system attacks the brain [and] other parts of the nervous system, leading to complications." Tr. 12. But Dr. Corbier did not explain what that would have entailed, nor did he provide any evidence supportive of his position that this situation actually occurred with Thomas. Further, the medical literature on which Dr. Corbier relied does not appear to speak to this theory.

(2) Direct Infection Theory

Dr. Corbier's second proposed mechanism of causation is direct infection. See Pet'rs' Ex. 20 at 2; Tr. 11-12. Dr. Corbier opined that Thomas's varicella vaccination could have caused either "a direct extension or direct primary infection" of his brain. Specifically, one can have an infection in either the dorsal root ganglia or the trigeminal nerve, which may result in "direct extension or direct primary infection" of the brain. Tr. 24. Dr. Corbier further opined that a direct infection of the brain may occur after a "live attenuated" vaccine. Tr. at 12. The "brain infection, in turn, irritates cortical brain cells resulting in a seizure disorder and other secondary neurological complications." Pet'rs' Ex. 20 at 2.

(3) Reactivation Theory

Dr. Corbier's third proposed mechanism of causation is "reactivation." Id. Dr. Corbier opined that it was "possible that Thomas may have had an initial mild or subclinical varicella infection" after his first varicella vaccination and that his second varicella vaccination caused reactivation of the infection, which caused his injuries. Id. at 4; see also Tr. 24-25. Dr. Corbier conceded that he was unaware of any conclusive evidence that Thomas had a varicella infection after his first varicella vaccination, Tr. 25-26, but he asserted that Thomas's clinical picture was consistent with this theory. See Pet'rs' Ex. 20 at 4.

(4) Medical Literature

Dr. Corbier cites several studies which support his opinion that individuals may develop an infection after a varicella vaccination, which can lead to the development of meningoencephalitis and resulting neurological complications, including seizures. Generally, these studies address the “direct infection” and/or “reactivation” theories of causation. See Pet’rs’ Ex. 11 at 34-35; Pet’rs’ Ex. 20 at 2-3.

Dr. Corbier cited the Chouliaras article, see Pet’rs’ Ex. 11 at 35, a case report of “an immunocompetent 3 ½-year-old girl who developed encephalitis and herpes zoster ophthalmicus 20 months after her immunization with varicella-zoster virus vaccine.” Pet’rs’ Ex. 38 at 1. “Molecular analysis confirmed the vaccine strain as the causative agent,” and not a wild-type virus. Id. The authors concluded that the “[VZV] vaccine strain may cause encephalitis in children even in the absence of underlying immunodeficiency.” Id. at 5 (emphasis added).

Dr. Corbier also referenced the Iyer article, see Pet’rs’ Ex. 20 at 3, where the authors described a case of “vaccine-associated aseptic meningitis after herpes zoster in a previously healthy child.” Pet’rs’ Ex. 19 at 1. The authors noted that “serious adverse events have occasionally been reported with vaccine-strain varicella-zoster virus,” and that the “varicella zoster virus has increasingly been implicated in central nervous system (‘CNS’) infections in immunocompetent individuals as well.” Id. at 1-2.

To further support his assertion that the “[v]aricella vaccination itself can cause neurological symptoms by causing meningitis,” Dr. Corbier cited the Levin case report, see Pet’rs’ Ex. 20 at 3, which describes a confirmed case of meningitis caused by a VZV vaccine in an immunocompetent child. Pet’rs’ Ex. 24 at 1.¹⁹ Fluid samples from the CSF and skin lesions of the child contained VZV from the varicella vaccine. Id. at 2. The authors of this article discussed a number of case reports previously documenting varicella vaccine-related injuries, including CNS disorders, meningitis, and encephalopathy. Id. at 1-3. The authors also indicated that reactivation of latent VZV can cause such injuries. Id. at 1.

Dr. Corbier also referenced the Chaves article. See Pet’rs’ Ex. 20 at 3 (citing Pet’rs’ Ex. 25²⁰). The authors of this article found that 5% of documented adverse events associated with the varicella vaccine (based on VAERS²¹ data) were “serious.” Pet’rs’ Ex. 25 at 1. These adverse events included meningitis, fever, encephalopathy, and seizures. Id. at 2-4.

¹⁹ Myron Levin et al., “Herpes Zoster with Skin Lesions and Meningitis Caused by 2 Different Genotypes of the Oka Varicella-Zoster Virus Vaccine,” 198(10) J. Infectious Diseases 1444 (2008).

²⁰ Sandra S. Chaves et al., “Safety of Varicella Vaccine after Licensure in the United States: Experience from Reports to the Vaccine Adverse Event Reporting System, 1995-2005,” 197 J. Infectious Diseases S170 (2008).

²¹ Vaccine Adverse Event Reporting System (“VAERS”).

Finally, Dr. Corbier referenced the Koskiniemi collaborative study,²² see Pet'rs' Ex. 20 at 3, which found that the "[v]aricella-zoster virus . . . was the main agent associated with encephalitis," in a study of "3231 patients with acute central nervous system . . . symptoms of suspected viral origin." Pet'rs' Ex. 27 at 1. The authors found that "VZV seems to have achieved a major role in viral infections of [the central nervous system]." Id.

b. Respondent's Expert, Dr. Holmes

Dr. Gregory Holmes, also a pediatric neurologist, testified on behalf of respondent. Tr. 83; Resp't's Ex. B (Dr. Holmes's curriculum vitae). At the time of the hearing, Dr. Holmes was transitioning from a full-time position at Dartmouth Medical School and Dartmouth-Hitchcock Medical Center, where he was the chair of the Department of Neurology, to the University of Vermont, where he is to become the chair of the Department of Neurological Sciences. Tr. 83-84. He is board-certified in pediatrics, neurology with special competence in pediatric neurology, electroencephalography, and clinical neurophysiology. Tr. 86; Resp't's Ex. B at 1. Dr. Holmes is licensed to practice medicine in Massachusetts, New Hampshire, and Vermont, and spends approximately 60% of his time treating patients. Tr. 86; Resp't's Ex. B at 1. Dr. Holmes estimated that he has treated five to seven patients for varicella encephalitis, and has seen "a lot of post-infectious varicella problems." Tr. 87-88. None of the patients, however, had developed varicella encephalitis secondary to a vaccine. Tr. 134. One of his over 300 publications is an article Dr. Holmes published in 1990 concerning a child who had varicella encephalitis. Tr. 89. Throughout his career, Dr. Holmes has won numerous awards and honors, primarily due to his research and work in the field of epilepsy. Resp't's Ex. B at 4-5.

Dr. Holmes asserted that Thomas's vaccination did not cause his injuries, although he agreed that the varicella vaccine can cause neurologic injuries, including those from which Thomas suffers. See Resp't's Ex. A at 8. Dr. Holmes agrees with Dr. Corbier that medical reports have documented a causal relationship between the varicella vaccine and encephalitis. See id. at 8; Tr. 116-18.

Dr. Holmes did not dispute Dr. Corbier's mechanism of direct infection. He testified that the varicella vaccine contains a live virus that "could invade the central nervous system" and cause encephalitis. Tr. 116; see also Resp't's Ex. C at 6²³ ("[central nervous system] complications of [VZV] infection include acute cerebellar ataxia, encephalitis, and vasculitis") (emphasis added); Resp't's Ex. E at 9²⁴ ("mild [varicella zoster virus] encephalitis associated with zoster probably exists"). Dr. Holmes also explained that a varicella infection is "usually quite benign" unless an individual is immunocompromised, which Thomas was not. Tr. 92. Although he considered it "[e]xtremely rare . . . in people that are not immunocompromised," Dr. Holmes agreed that the varicella vaccine can cause an individual to develop both encephalitis and an encephalopathy through a direct or primary varicella infection. Tr. 116-17. He based

²² Marjaleena Koskiniemi et al., "Infections of the central nervous system of suspected viral origin: A collaborative study from Finland," 7 J. NeuroVirology 400, 400 (2001).

²³ Henry J. Baskin & Gary Hedlund, "Neuroimaging of herpesvirus infections in children," 37 *Pediatr Radiol.* 949, 954 (2007).

²⁴ Don Gildea et al., "Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment," 8(8) *Lancet Neurology* 731 (2009).

this statement, in part, on his own experience with patients who developed encephalitis as a result of a direct varicella infection.²⁵ Tr. 128.

Dr. Holmes also agreed with Dr. Corbier's mechanism of reactivation. See Tr. 109-11. Dr. Holmes testified that an individual could develop encephalitis and/or an encephalopathy as a result of a reactivated varicella infection. Tr. 115-17; see also Tr. 127-28. He recognized that the Institute of Medicine ("IOM") found "evidence supporting a causal relationship between varicella vaccine and vaccine-strain viral re-activation with subsequent infection resulting in . . . encephalitis." Resp't's Ex. A at 9.

Dr. Holmes did not believe that Dr. Corbier's theory of causation based on an autoimmune response theory was plausible. Tr. at 112.

c. Evaluation of the Evidence

Respondent's expert, Dr. Holmes, does not dispute Dr. Corbier's proposed mechanisms of direct infection and reactivation. See Tr. 115-19; Resp't's Ex. A at 7. Dr. Holmes also does not dispute that the varicella vaccine can cause a vaccine to develop encephalitis and/or encephalopathy. Tr. 117-18.

Case reports, such as those on which Dr. Corbier relies, may be helpful for petitioners in Vaccine Program cases to establish causation by a preponderance of the evidence. See, e.g., Roper v. Sec'y of Health & Human Servs., No. 00-407V, 2005 WL 3597255, at *5 (Fed. Cl. Spec. Mstr. Dec. 9, 2005); Stevens v. Sec'y of Health & Human Servs., No. 99-524V, 2006 WL 659525, at *22-24 (Fed. Cl. Spec. Mstr. Feb. 24, 2006). The medical literature referenced by respondent's expert in his expert report provides further support for petitioners' theories of causation. Specifically, Dr. Holmes quoted the 2012 IOM report, which states that "[t]he evidence convincingly supports a causal relationship between varicella vaccine and vaccine-strain viral re-activation with subsequent infection resulting in meningitis or encephalitis."²⁶ (emphasis added). See also Pet'rs' Ex. 19 at 3 (the varicella "vaccine is composed of a live attenuated virus with the potential for reactivation and complications in both immunocompetent and immunocompromised hosts.").

The literature relied on by the parties' experts establishes that the varicella vaccine could have caused Thomas's injuries in a manner consistent with Dr. Corbier's theories of direct infection and reactivation. Dr. Holmes does not dispute the two theories of causation—direct infection and infection reactivation. Accordingly, petitioners have met their burden under Althen Prong One.

ii. Althen Prong Two: Logical Sequence of Cause and Effect

Under Althen Prong Two, petitioners must prove "a logical sequence of cause and effect showing that the vaccination was the reason for [Thomas's] injury." Althen, 418 F.3d at 1278.

²⁵ Dr. Holmes clarified that these individuals' varicella infections were not vaccine-related. Tr. 128.

²⁶ IOM (2012), at 267.

This requires petitioners to show that the vaccine Thomas received actually caused the alleged injury. Pafford, 451 F.3d at 1354. Petitioners need not make a specific type of evidentiary showing. That is, petitioners are not required to offer “epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect.” Capizzano, 440 F.3d at 1325. Instead, petitioners may satisfy their burden by presenting circumstantial evidence and reliable medical opinions. See id. at 1325-26.

a. Petitioners’ Expert, Dr. Corbier

Dr. Corbier opines that there is a logical sequence of cause and effect between Thomas’s vaccination and his encephalitis. Tr. 12. First, Dr. Corbier states that Thomas exhibited signs and symptoms of an infectious process shortly after his second varicella vaccination on October 2, 2008, including blisters, fever, and seizures. Pet’rs’ Ex. 18 at 34; see also Tr. 11-13, 24-26. Dr. Corbier testified that:

Well, the logical sequence is that a young child is given a live attenuated vaccine. The vaccine is shown under –based on the information that we have in rare cases to in some patients lead to certain neurological complications. We know that Thomas was given two doses [of the varicella vaccine] that were fairly close together and . . . two weeks later he developed blisters and other changes to suggest that perhaps he developed complications from the varicella vaccine. So I believe there is a logical sequence there of events.

Tr. 12. Dr. Corbier also asserts that diagnostic tests did not rule out that a varicella virus was the cause of Thomas’s injuries, and there was no other explanation for his illness. Tr. 60. Lastly, Dr. Corbier considers Thomas’s time frame from the date of vaccination to onset of his illness to be consistent with the clinical course of a varicella infection. Pet’rs’ Ex. 20 at 3-4. Dr. Corbier concludes that more likely than not that the vaccine was the cause of Thomas’s encephalopathy. Pet’rs’ Ex. 18 at 1; Tr. 46. As discussed below, the medical literature Dr. Corbier referenced supports these aspects of his opinion.

With regard to the issue of blisters, Thomas’s medical records indicate that he exhibited blisters and/or lesions around his lips, mouth, and left ear after he received his subject vaccination. See Pet’rs’ Ex. 8 at 305; Pet’rs’ Ex. 10 at 214, 229. Thomas’s treating physician, Dr. Ahmed, thought the blisters were “suggestive of herpes.” Pet’rs’ Ex. 10 at 230. Dr. Corbier considers the blisters that Thomas developed to be signs and symptoms of a vaccine-induced infectious process. Tr. 12-13, 26. While Dr. Corbier believed that the blisters were caused by a varicella infection, he agreed that the blisters could also be consistent with many other viral infections. Tr. 27, 58-59.

Several of the case reports referenced by Dr. Corbier described patients with varicella-induced encephalitis who had lesions similar to Thomas’s blisters. Because Thomas’s lesions were not scraped and sent for PCR testing, there is no definitive evidence of etiology. Tr. 20. The presence of these blisters, however, provides circumstantial evidence of a varicella infection, as testified to by Dr. Corbier, and as supported by the medical literature.

For instance, in the Chouliaras case report, a 3½-year-old immunocompetent girl developed varicella vaccine-associated encephalitis. Pet’rs’ Ex. 38 at 2. At the onset of her condition, she presented with a “herpetiform rash on the right side of her face . . . and herpetic lesions.” Id. Similarly, in the Fusco case report, the authors presented findings of a 79-year-old woman who suffered from “varicella meningitis/encephalitis coincident with vaccination,” and who developed “scattered vesicular lesions on her right ear, left cheek, left lower quadrant and right lower back.” Pet’rs’ Ex. 39 at 1.²⁷ The Levin case report also documented an immunocompetent eight-year-old boy, who suffered from varicella vaccine-associated meningitis and developed a rash on his shoulder, which “evolved into multiple small vesicles over . . . 2 days.” Pet’rs’ Ex. 24 at 1. During the following week, “[m]ultiple lesions on the left arm and shoulder [became] scabbed.” Id. at 2.

Thomas’s symptoms also included fever, which was an important fact to Dr. Corbier. Pet’rs’ Ex. 20 at 1. On October 16, 2008, Thomas’s fever at the pediatrician’s office was 100.9°F and increased to 104.4°F. Pet’rs’ Ex. 8 at 75-76.

In addition to blisters and fever, Thomas also presented with seizures. The seizures provide a basis for Dr. Corbier’s opinion. Pet’rs’ Ex. 20 at 1; Tr. 13. Dr. Holmes agreed that a child with varicella encephalitis could present with seizures. Tr. 114.

Dr. Corbier also based his causation opinion on the fact that Thomas had “an extensive workup which included lumbar puncture, neuroimaging, and various labs, was diagnosed with meningoencephalitis . . . and had evidence of hepatitis,” and that there was no other viral explanation found for his illness.” Pet’rs’ Ex. 20 at 1. Various viruses were ruled out during Thomas’s hospitalization, including HSV, EBV, LMCV, adenoviruses, Bartonella, and Arbovirus. Pet’rs’ Ex. 10 at 239-47, 255; see also Pet’rs’ Ex. 20 at 7. There is no evidence to suggest that Thomas was exposed to any virus other than the VZV within a medically appropriate time frame.

Dr. Corbier agreed that Thomas’s oropharynx swab test did not contain evidence of a varicella infection, which would have been an “ideal situation” for a diagnosis of varicella infection, but he did not consider it a necessary diagnostic criterion. Tr. 40-41. He also suggested that the acyclovir treatment could have affected the accuracy of the swab test results. Tr. 61-62. Of note, in the Koskiniemi case study, throat cultures, like the oropharynx swab done on Thomas, which was negative, had a “poor yield.” Pet’rs’ Ex. 27 at 4.

Thomas’s initial MRI conducted on October 17, 2008, was normal. The results of his later MRIs showed diffuse edema, “diffuse cerebral atrophy of the brain,” and hypoxic injury. Tr. 35-36, 53. Dr. Corbier opined that while the results of Thomas’s October 28, 2008 MRI did not conclusively demonstrate that Thomas suffered from a varicella infection, see Tr. 39, they “[don’t] go one way or the other as far as a differential diagnosis,” Tr. 39, and emphasized at the hearing that MRI findings vary in patients with varicella infections. See Tr. 35.

²⁷ Dahlene Fusco et al., “VZV meningitis following varicella vaccine,” 48(4) J. Clinical Virology 275, 275 (2010).

Lastly, Dr. Corbier considered the time frame within which Thomas's injuries manifested after his vaccination as strong support for his opinion that they are vaccine-related. Tr. 44-45. (This aspect of Dr. Corbier's opinion is discussed in more detail below.) Thomas rapidly became more ill and "quickly went on to develop severe epilepsy and global devastation." Tr. 13. Based on the timeline, Dr. Corbier opined that Thomas's clinical course provided circumstantial evidence of a "clear-cut event" of vaccine-induced harm. Tr. 13.

Dr. Corbier was questioned regarding his consultation with Dr. Rupar. Tr. 31-32. He did not meaningfully expound on his disagreement with Dr. Rupar's opinion that Thomas's injuries were not vaccine-related.²⁸ Tr. 32.

This logical sequence of cause and effect described by Dr. Corbier, where the vaccination led to an infection followed by neurological complications, is most consistent with either the direct infection or reactivation theories of causation. Tr. at 12-13; 24; 142-43.

b. Respondent's Expert, Dr. Holmes

Dr. Holmes agrees that Thomas's injuries are most likely the result of a viral infection. Tr. 143. Although Dr. Holmes argued that Thomas's clinical course was inconsistent with a varicella infection secondary to the vaccine, he provided little supportive evidence for his opinion. Dr. Holmes referenced the IOM report and three medical articles, which generally concerned his interpretation of Thomas's MRIs. See Resp't's Ex. A at 7 (citing Resp't's Exs. C, E, F²⁹).

Dr. Holmes disputed both the soundness and the applicability of Dr. Corbier's mechanisms of causation to Thomas's case, as well as the medical literature on which Dr. Corbier relied to support his opinions. See id. at 7-10. As to the causal mechanisms proposed by Dr. Corbier, Dr. Holmes first asserted that the "autoimmune" mechanism of causation did not occur in Thomas's case. He opined that an "autoimmune response to the varicella infection or vaccine would [have] be[en] much different" than what occurred in Thomas's case. Tr. 112; see

²⁸ Because Dr. Rupar was one of Thomas's treating physicians, the undersigned has given Dr. Rupar's opinion careful consideration. Capizzano, 440 F.3d at 1326 (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 1279). His view, however, is not dispositive and can be rebutted. See Snyder v. Sec'y of Health & Human Servs., 88 Fed. Cl. 706, 745 n.67 (2009). Dr. Rupar did not explain the basis of his opinion that Thomas's encephalitis was not vaccine-related. He stated that "there [was] no evidence" to suggest otherwise and that varicella encephalitis "is usually not that severe and should not occur . . . [after a] second shot preferentially." Pet'rs' Ex. 10 at 2675. Because Dr. Rupar did not testify at the hearing, it is difficult to assess the basis of his opinion. See Perreira, 33 F.3d at 1377 n.6 ("[a]n expert opinion is no better than the soundness of the reasons supporting it"). Likewise, it is difficult to assess Dr. Corbier's limited explanation for his disagreement with Dr. Rupar's opinion.

²⁹ Elena Miravet et al., "Clinical and radiological features of childhood cerebral infarction following varicella zoster virus infection," 49 *Developmental Med. & Child Neurology* 417 (2007).

also Tr. 142-43. Dr. Holmes did not expound on what that autoimmune response would have entailed.

Second, Dr. Holmes opined that a primary varicella infection is generally benign in immunocompetent children, but can be “serious and life-threatening” in immunocompromised individuals. Id. The parties did not dispute that Thomas is immunocompetent. Thus, according to Dr. Holmes, it is unlikely that Thomas’s injuries constitute a reaction to the VZV because such reactions are “[e]xtremely rare” in immunocompetent individuals. Tr. 117. Dr. Holmes conceded, however, that the medical literature describes cases of VZV after vaccination in immunocompetent children. Tr. 138; see also supra Section III(B)(i)(a)(4).

Dr. Holmes considered Thomas’s clinical course to be atypical of a primary (direct) varicella infection in a number of ways. Resp’t’s Ex. A at 7. Dr. Holmes opined that a varicella infection initially causes infected individuals to suffer from a headache, fever, malaise, and a “characteristic skin rash.” Id. at 8. When questioned, however, Dr. Holmes agreed that Thomas did have these signs and symptoms.

Dr. Holmes noted that patients with varicella infections generally present first with “constitutional symptoms such as fever [and] irritability.” Tr. 93, 129. Dr. Holmes also testified that Thomas did have malaise and, in fact, was very sick. Tr. 140. As for fever, Dr. Holmes conceded that Thomas did have fever, although Dr. Holmes described it as intermittent. Tr. 93, 139. He explained that there was no particular type of fever specific to varicella infection, that is, the fever could be low- or high-grade. Tr. 138. The literature Dr. Corbier referenced demonstrates that Dr. Holmes is correct. Compare Pet’rs’ Ex. 24 at 1 (patient with varicella infection developed a low-grade fever) with Pet’rs’ Ex. 35 at 1³⁰ (patient with varicella infection developed a high-grade fever); see also Pet’rs’ Ex. 25 at 2-4 (authors found fever to be a common symptom of varicella infection); Pet’rs’ Ex. 34 at 1³¹ (patient with varicella infection developed fever).

Dr. Holmes’s testimony regarding the CSF findings is supportive of petitioners’ position. Dr. Holmes testified that Thomas’s CSF test results from October 16, 2008, were “quite abnormal,” indicating an inflammatory response seen in “severe encephalitis.” Tr. 95. Dr. Holmes testified that the CSF test results were consistent with inflammation and an infectious process consistent with varicella. Tr. 132. Based upon literature filed by both experts, patients with a varicella infection generally present with CSF pleocytosis.³² See Resp’t’s Ex. E at 1. “Many patients also have red blood cells in their CSF.” Id. at 3; see also Pet’rs’ Ex. 38 at 8. Thomas presented with pleocytosis and had elevated WBCs, RBCs, and segs. Id.

Dr. Holmes testified that Thomas’s blisters were uncharacteristic of a varicella infection because the blisters were not more widespread. See Tr. 93. Dr. Holmes did agree with Dr.

³⁰ Elena Chiappini et al., “Varicella-zoster virus acquired at 4 months of age reactivates at 24 months and causes encephalitis,” 140(2) J. Pediatrics (2002).

³¹ Ronen Spiegel et al., “Severe Meningoencephalitis Due to Late Reactivation of Varicella-Zoster Virus in an Immunocompetent Child,” 25(1) J. Child Neurology 87 (2010).

³² Pleocytosis is the “presence of a greater than normal number of cells in the cerebrospinal fluid.” Dorland’s at 1460.

Corbier's description of the blisters or rash. The rash was on Thomas's lips and ear. Tr. 141. But, according to Dr. Holmes, Thomas only had "limited skin exposure," Resp't's Ex. A at 7, and only developed two oral lesions, which Dr. Holmes considered atypical of a varicella infection. Id. at 8; see also Tr. 140. Dr. Holmes also opined that varicella infections typically present with "crops" of lesions that "start off with some red bumps, and . . . become vesicles and then would crust over." Tr. 93. The basis of Dr. Holmes's testimony that Thomas only had two oral lesions is unclear. The description in the medical records of multiple ulcers, however, is more suggestive of "crops" of lesions than just two lesions. The medical records document that Thomas had "multiple ulcers" on his lips. Pet'rs' Ex. 10 at 269. "Multiple ulcers" suggests that there may be more than two lesions. Also, the lesions were described by the treating physicians as "herpetic." This suggests that the lesions were caused by a virus in the herpes family, like VZV.

Although he agreed that the rash was viral, Dr. Holmes did not, however, believe it was specific for the VZV. Tr. 142. Dr. Holmes testified that it is now recommended that a PCR test be done on skin lesions to diagnose etiology. Tr. 105. Dr. Holmes verified that the PCR test was not performed on Thomas's lesions. Tr. 105.

Third, in his report, Dr. Holmes stated that Thomas's MRIs were uncharacteristic of varicella encephalitis because they showed a "diffuse cerebral edema suggestive of a toxic or anoxic encephalopathy and did not suggest a VZV vasculitis." Resp't's Ex. A at 7. Citing two articles,³³ Dr. Holmes opined that "[v]aricella encephalitis consists of medium to large vessel vasculopathies³⁴ with ischemic or hemorrhagic strokes."³⁵ Id. Dr. Holmes pointed out that the results of Thomas's MRIs did not provide evidence of vasculitis or stroke, which are typically found in subjects with varicella-induced encephalitis. Tr. 100. Dr. Holmes explained that "[v]aricella encephalitis is particularly prone to causing a vasculitis,"³⁶ which can cause both major and minor strokes throughout the brain. Tr. 95-96. Because Thomas did not have evidence of vasculitis on his MRIs, Dr. Holmes opined that this further suggested Thomas did not have varicella encephalitis. Tr. 99.

Dr. Holmes also testified, however, that Thomas's MRI done on October 28, 2008, showed edema and evidence of prolonged seizures. Tr. 101. Dr. Holmes explained that "[e]dema is swelling . . . It's just too much fluid in the brain," which can be caused by "an infection or any kind of metabolic insult, trauma, a whole variety of things." Tr. 100.

Dr. Holmes further testified as follows:

The edema that you can see [in Thomas's MRI] can be from an infection. It can also be seen . . . with frequent seizures, and . . . prolonged seizures especially can give you a

³³ Resp't's Ex. C and Resp't's Ex. F.

³⁴ A vasculopathy is "any disorder of the blood vessels." Dorland's at 2026.

³⁵ An ischemic stroke is "caused by ischemia of an area of the brain." Id. at 1786. Ischemia is "deficiency of blood in a part, usually due to functional constriction or actual obstruction of a blood vessel." Id. at 961.

³⁶ Dr. Holmes described vasculitis as "an inflammatory response causing lack of blood through the blood vessels." Tr. 96.

pattern very similar to this, and it can look like hypoxic injury, but it's just due to the excessive excitation of brain cells that are firing when they should not.

Tr. 101.

Thus, Dr. Holmes's testimony supports a conclusion that Thomas's MRI is actually consistent with edema caused by infection and evidence of prolonged seizures. The Baskin article cited by Dr. Holmes states that a varicella infection can cause cerebellitis,³⁷ edema, *or* stroke. Resp't's Ex. C at 8. Thus, edema can be seen in varicella infections, and MRI findings of vasculitis are not always present.

Fourth, Dr. Holmes considered it "very unlikely in a child who has had a prior varicella immunization to have a severe primary infection with a second immunization since some immunity is likely to have occurred with the initial vaccination." Resp't's Ex. A at 7. This statement seems to ignore the theory of reactivation, which Dr. Holmes agrees is medically plausible. See Tr. 142.

The fifth basis of Dr. Holmes's opinion is that no virus was isolated in Thomas's October 18, 2008 oropharynx swab test. Resp't's Ex. A at 8. In Dr. Holmes's view, Thomas's treating physicians "were screening for anything that could be detected by the swab," but found nothing. Tr. 105. Citing a CDC report,³⁸ Dr. Holmes opined that there would have been positive evidence of varicella in the swab test results had Thomas suffered from a varicella infection, but he noted that the results were negative. Resp't's Ex. A at 7; Tr. 105. He also stated, however, that the oropharynx swab test was not conclusive and that the test was not as accurate as other tests that could have been performed. Tr. 143-44.³⁹ Dr. Holmes explained that a PCR test for varicella would have provided "more specific" results, but noted that it was not performed on Thomas. Tr. 105-06. Polymerase chain reaction ("PCR") testing of the CSF and/or scrapings from skin lesions can be performed for a near-definitive diagnosis of VZV. Resp't's Ex. C at 2; Pet'rs' Ex. 19 at 3.

Lastly, Dr. Holmes stated that there are numerous other viral causes of encephalitis that present with a clinical picture similar to that of Thomas's, Resp't's Ex. A at 8, and that not identifying a specific causal agent, as occurred in Thomas's case, is not unusual.

Dr. Holmes was unaware of any of his patients with a varicella infection who also had a concurrent hepatitis infection like Thomas. Tr. 110-11. Dr. Holmes, however, agreed that hepatitis, like Thomas had, can be seen with direct infection by varicella infections. Tr. 131-32; see also Resp't's Ex. D at 239 ("Possible complications from varicella infection include . . . transient hepatitis.").

³⁷ Cerebellitis is "inflammation of the cerebellum." Dorland's at 332.

³⁸ Centers for Disease Control and Prevention, "Chapter 22: Laboratory Support for Surveillance of Vaccine-Preventable Diseases," available at <http://www.cdc.gov/vaccines/pubs/surv-manual/chpt22-lab-support.html>. Although Dr. Holmes provided a link to this source in his report, respondent did not file the site's contents as an exhibit.

³⁹ The authors of the Koskiniemi study noted that throat samples like the oropharynx swab test here gave a poor diagnostic yield. Pet'rs' Ex. 27 at 4.

With regard to the seizures, Dr. Holmes agreed that the majority of pediatric patients who have varicella encephalitis present with seizures. Tr. 130. In his experience, some patients had focal seizures with focal processes seen on CT scan, and the other children had “evidence of multifocal disease.” Tr. 130. Dr. Holmes testified that multifocal disease is characterized by seizures coming from different areas of the brain, as determined by EEG. Tr. 131.

c. Evaluation of the Evidence

The undersigned evaluates the parties’ respective experts’ opinions based on the record as a whole, including the medical literature on which they relied in formulating their opinions, as well as Thomas’s medical records. Snyder, 88 Fed. Cl. at 742-43 (special masters are not required to accept the ipse dixit of an expert) (citing General Electric Co. v. Joiner, 522 U.S. 136, 146 (1997)).

There is no conclusive evidence in the record that demonstrates Thomas suffered from a varicella infection. The parties’ experts agree that a PCR test would have been the most accurate method to determine whether Thomas actually suffered a varicella infection, but this test was not performed. See Pet’rs’ Ex. 19 at 2 (a “real-time [PCR test] is currently considered to be the most widely accepted method for the diagnosis of viral meningoencephalitis”). Because no conclusive testing was performed, the record evidence regarding whether Thomas did, in fact, suffer a varicella infection is necessarily circumstantial.

Dr. Corbier’s opinion regarding causation is straightforward. After receiving the varicella vaccine, with a live attenuated virus, Thomas developed a varicella infection, either through direct infection or reactivation, which caused encephalitis. He then developed severe epilepsy and global neurological devastation.

Dr. Holmes consistently maintained that Thomas’s clinical history was inconsistent with a typical varicella infection. Thomas’s clinical course, however, appears consistent with Dr. Corbier’s opinions and the medical literature. Thomas had herpetic type mouth and ear blisters and seizures. Pet’rs Ex. 8 at 75-76. He also had a fever and malaise. The MRI showed diffuse edema, which is consistent with a varicella infection, and Dr. Holmes agreed Thomas’s CSF analysis was also consistent with an inflammatory and infectious process that could occur due to a varicella infection. Tr. 132. Dr. Holmes also agreed that Thomas presented with seizures, consistent with a varicella infection. Tr. 130. Lastly, the parties agreed that Thomas’s injuries manifested within a time frame consistent with varicella infection. See Pet’rs’ Ex. 20 at 3-4; Tr. 137.

It is uncontested that Thomas was exposed to varicella through the vaccination, and the treating physicians and experts agree that his encephalitis is most likely due to a viral infection. As discussed, Thomas’s clinical course was consistent with viral encephalitis, and there is no evidence of exposure to any other virus that would have caused it. The most likely viruses were tested for and ruled out, except that no specific testing was performed for the VZV. The only known virus to which Thomas was exposed was the VZV contained in his subject vaccination.

All of these factual findings provide sufficient circumstantial evidence for the undersigned to conclude that Thomas's subject vaccine more likely than not caused his encephalitis and resultant injuries. See Capizzano, 440 F.3d at 1325 (circumstantial evidence may satisfy a petitioner's burden of proof under Althen). Accordingly, petitioners have met their burden under Althen Prong Two.

iii. Althen Prong Three: Timing

Under Althen Prong Three, petitioners must establish that Thomas's injury occurred within a time frame that is medically appropriate for the alleged mechanism of harm. See Pafford, 451 F.3d at 1358 ("Evidence demonstrating petitioner's injury occurred within a medically acceptable time frame bolsters a link between the injury alleged and the vaccination at issue under the 'but-for' prong of the causation analysis."). Petitioners may satisfy this prong by producing "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." de Bazan v. Sec'y of Health & Human Servs., 539 F.3d 1347, 1352 (Fed. Cir. 2008).

Petitioners may meet their burden by showing: (1) when the condition for which they seek compensation first appeared after vaccination, and (2) whether the period of symptom onset is "medically acceptable to infer causation." Shapiro v. Sec'y of Health & Human Servs., No. 99-552V, 2011 WL 1897650, at *13 (Fed. Cl. Spec. Mstr. Apr. 27, 2011), aff'd in relevant part and vacated on other grounds, 101 Fed. Cl. 532, 536 (2011), aff'd 503 F. App'x 953 (2013) (per curiam). The appropriate temporal association will vary according to the particular medical theory advanced in the case. See Pafford, 451 F.3d at 1358.

a. Petitioners' Expert, Dr. Corbier

Dr. Corbier opined that 14 days after Thomas received the second dose of the varicella vaccine, Thomas started having symptoms, including blisters, fever, mouth pain, and seizures. Pet'rs' Ex. 20 at 3. Dr. Corbier described this as a "clear-cut event" two weeks after Thomas received the vaccine. Tr. 13. Dr. Corbier cites to medical literature to support his opinion as to the appropriateness of this time interval. The Grossberg article outlines a case of a sixteen-year-old who developed a severe varicella infection 15 days after receiving a varicella vaccine. Pet'rs' Ex. 28 at 1.⁴⁰ The Chaves article notes that the medical interval between vaccination and the onset of rash was 23 days, with a range of 6 to 43 days. Pet'rs' Ex. 25 at 8; see also Pet'rs' Ex. 36 at 4⁴¹ ("The incubation is 14 to 16 days but may be as early as 10 or as late as 21 days after contact."); Pet'rs' Ex. 37 at 1⁴² (incubation period for VZV is 10 to 21 days).

⁴⁰ Richard Grossberg et al., "Secondary Transmission of Varicella Vaccine Virus in a Chronic Care Facility for Children," 148 J. Pediatrics 842 (2006).

⁴¹ June M. Caruso et al., "Central Nervous System and Renal Vasculitis Associated With Primary Varicella Infection in a Child," 107 Pediatrics (2001).

⁴² Izikson Leonid & Lilly Evelyn, "Primary Varicella in an Immunocompetent Adult," 2(8) J. Clinical & Aesthetic Dermatology 36 (2009).

b. Respondent's Expert, Dr. Holmes

Dr. Holmes agreed with Dr. Corbier that Thomas's injury occurred within an appropriate time frame after vaccination. Dr. Holmes testified that a child who developed an encephalopathy as a result of the varicella infection would display symptoms within 10 to 21 days after receipt of the vaccine, which is "similar to the incubation period" of varicella. Tr. 119-20.

c. Evaluation of the Evidence

Both parties' experts gave consistent opinions as to the expected time frame between vaccine and illness, i.e., 10-21 days. Thomas received the second varicella vaccine on October 2, 2008, and presented to his pediatrician's office on October 16, 2008, with fever, mouth lesions, and seizures. This 14-day time frame is medically appropriate. Petitioners have satisfied their burden of presenting preponderant evidence of Althen Prong Three.

iv. Alternative causation

Because the undersigned concludes that petitioners have established a prima facie case, they are entitled to compensation unless respondent can put forth preponderant evidence "that [Thomas's] injury was in fact caused by factors unrelated to the vaccine." Whitecotton v. Sec'y of Health & Human Servs., 17 F.3d 374 (Fed. Cir. 1994), rev'd on other grounds sub nom., Shalala v. Whitecotton, 514 U.S. 268 (1995); see also Walther v. Sec'y of Health & Human Servs., 485 F.3d 1146, 1151 (Fed. Cir. 2007).

Thomas's treating physicians, petitioners' expert witness, Dr. Corbier, and respondent's expert witness, Dr. Holmes, all agree that Thomas most likely had viral encephalitis. The issue is what specific virus was the instigator. Tests were ordered, however, which ruled out many suspected viruses, including enterovirus, HSV, EBV, LMCV, adenoviruses, Bartonella and arbovirus. Pet'rs' Ex. 10 at 239-47, 255. Moreover, there is no evidence to suggest that Thomas was exposed to any virus other than VZV within a medically appropriate time frame.

Dr. Holmes testified that some other virus was the likely cause of Thomas's illness. Tr. 143. Dr. Holmes also testified that in up to 80% of encephalitis cases there is no diagnosis of a particular viral causal agent. Tr. 108. But he did not provide medical literature or other support for the proposition that another virus caused Thomas's injuries. In contrast, petitioners submitted the Koskiniemi article, a study of 3231 patients with acute CNS symptoms with suspected viral causes. Pet'rs' Ex. 27 at 1. Upon investigation, 46% of the patients had a viral cause. Id. Of those 46%, the varicella virus was responsible for 29% of CNS illnesses. Id. While the Koskiniemi study was done during 1995-1996, a pre-varicella vaccine time frame, the 2009 Iyer study found that VZV was responsible for 11% of meningitis cases in adults. Pet'rs' Ex. 19 at 2. The Iyer article emphasized the increasing importance of testing for VZV, especially in patients with skin lesions suggestive of varicella. Id. at 3. Unfortunately, that testing was not done for Thomas. Simply stated, petitioners set forth a prima facie case, and respondent failed to rebut it.

IV. Conclusion

For the reasons discussed above, the undersigned finds that petitioners are entitled to compensation because they have provided sufficient circumstantial evidence that preponderates in their favor. A separate damages order will issue.

IT IS SO ORDERED.

s/ Nora Beth Dorsey
Nora Beth Dorsey
Special Master