In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 99-946V

Filed: August 13, 2015

* *	**To Be Published**
SHON SUMNER, for herself and on behalf of her daughter, S.E.B., and JONATHAN BURCH, on his own behalf and on behalf of his daughter,	Special Master Hamilton-Fieldman
Petitioners,	Causation; Measles-Mumps-Rubella ("MMR") Vaccine;
v.	Congenital Rubella syndrome ("CRS"); Aicardi syndrome
SECRETARY OF HEALTH AND HUMAN SERVICES,	("AS"); Reliability of Expert Methodology.
Respondent.	
* *	

Clifford Shoemaker, Shoemaker and Associates, Vienna, VA, for Petitioners.
Lisa Ann Watts, United States Department of Justice, Washington, DC, for Respondent.

DECISION[1]

Petitioners, Shon Sumner[2] and Jonathon Burch, filed this vaccine claim under the National Vaccine Injury Compensation Program ("the Program")[3] on behalf of their minor

[1] The undersigned intends to post this order on the United States Court of Federal Claims website, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, § 205, 116 Stat. 2899, 2913 (codified as amended at 44 U.S.C. § 3501 note (2012)). As provided by Vaccine Rule 18(b), 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). Otherwise, "the entire" order will be available to the public. *Id.*

[2] On November 17, 2011, the Special Master previously assigned to this case granted Petitioners' motion to amend the case caption. *See* Order, filed November 17, 2011, at 1. The caption was amended to reflect the fact that Shon Burch's name had been changed to Shon Sumner. *Id*.

[3] The Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 *et seq.* [hereinafter

daughter, S.E.B., on November 19, 1999. Petitioners allege that, as a result of the administration of a Measles-Mumps-Rubella ("MMR") vaccine on March 25, 1996, while Shon Sumner ("Ms. Sumner") was pregnant with S.E.B., S.E.B. suffered from brain malformation, hydrocephalus, seizures and developmental delays. Petition at 1-2; Petitioners' Exhibit ("Pet. Ex.") 1 at 2. At the outset of the November 22, 2013 entitlement hearing, Petitioners clarified their causation theory, which is that only the rubella component of the MMR vaccine had been causal: the rubella component had caused S.E.B. to suffer from a partial rubella infection *in utero*; and the infection manifested, after S.E.B. was born, as Aicardi syndrome ("AS" or "Aicardi").[4] Transcript ("tr.") at 52.

The undersigned now finds that Petitioners have failed to prove, by a preponderance of the evidence, that S.E.B.'s injuries resulted from the administration of the MMR vaccine to Ms. Sumner during pregnancy. The Clerk's Office is ordered to enter judgment in favor of Respondent unless a motion for review is filed.

I. Facts

Ms. Sumner delivered her first child on December 7, 1995, via cesarean section. Pet. Ex. 5 at 65. The child, S.E.B.'s older sibling, was born full-term, and no congenital abnormalities were noted. *See* Ex. 5 at 65.

S.E.B. appears to have been conceived in early 1996; Ms. Sumner's last known menstrual period is alternatively dated February 15th and February 17th, 1996. Tr. at 157; *see also* Pet. Ex. 5 at 19; Pet. Ex. 3 at 57. The parties agree that, on March 25, 1996, the date she received the MMR vaccine at issue, Ms. Sumner was in the first trimester of her pregnancy. Pet. Ex. 1 at 2;[5] *see also* tr. at 48. The parties disagree, however, as to S.E.B.'s exact gestational age at the time of vaccination. Dr. Gerald Raymond has opined that, based on the date of the last recorded menstrual period, the "confirmatory measurements performed during the pregnancy by ultrasound, and the actual delivery date of a fullterm infant would place this immunization at approximately 26 days after conception." Respondent's Exhibit ("Resp. Ex.") A at 1. Dr. Joseph Bellanti has opined that Ms. Sumner received the vaccination "approximately 2 months into her second pregnancy with [S.E.B.]." Pet. Ex. 12 at 3.

"Vaccine Act" or "the Act"]. Hereafter, individual section references will be to 42 U.S.C. § 300aa of the Act.

[4] Aicardi syndrome is "a syndrome affecting female infants, characterized by agenesis of the corpus callosum, large discrete areas of chorioretinopathy, spasms and tonic seizures, and mental retardation." *Dorland's Illustrated Medical Dictionary* ("*Dorland's*"), 1820 (32nd ed. 2012).

[5] According to her immunization record, Ms. Sumner had been administered another MMR vaccination almost 20 years prior, on September 2, 1977. Pet. Ex. 1 at 2.

Ms. Sumner's first prenatal visit took place on August 19, 1996, approximately 27 weeks into her pregnancy. Pet. Ex. 3 at 57-59. Ultrasounds performed on August 28, 1996 and November 6, 1996 were unremarkable. Pet. Ex. 5 at 22-23.

S.E.B. was born on November 21, 1996, at Taylor Regional Hospital in Hawkinsville, Georgia, at approximately 40 weeks gestation. Pet. Ex. 2 at 8, 41; *see also* Pet. Ex. 6 at 4 (noting that S.E.B.'s gestational age at birth was "approximately 38 weeks"). Delivered by repeat cesarean due to cephalopelvic[6] disproportion and ineffectual induced labor, S.E.B. weighed seven pounds, nine ounces; her APGAR scores were 8 and 9. Pet. Ex. 3 at 23-24, 45-46. Upon discharge from the hospital, S.E.B. was noted to be large for her gestational age and macrocephalic.[7] Pet. Ex. 6 at 4. A neonatal sonogram was performed on November 23, 1996, when S.E.B. was two days old, and showed that S.E.B. had enlarged brain ventricles and possible associated cerebral or mid-brain abnormalities. Pet. Ex. 2 at 21. That same day, S.E.B. was transferred to Columbia Coliseum Medical Centers ("CCMC") for evaluation of possible hydrocephalus. Pet. Ex. 6 at 4.

While at CCMC, S.E.B. received a hearing screening, a computerized tomography ("CT") scan, and a cranial ultrasound. Pet. Ex. 6 at 4-5, 25-27. She was discharged with a diagnosis of hydrocephalus ex vacuo[8] with "insult occurring possibly *in utero*," and was noted to have had an absent corpus callosum. *Id*. at 4-5. An eye examination revealed hypoplasia of the optic nerves with retinal hypertrophy, dysgenesis and macular sparing. *Id.* at 9. Serology reports showed a normal complete blood count; "[c]ord blood IGM[9] was within normal limits."[10] Pet. Ex. 6 at 4, 15-17, 32. She had positive IgG[11] titers to rubella at 2.49(k) and herpes type 1 at 3.25(f), and negative titers to toxoplasmosis and Cytomegalovirus ("CMV"). *Id.* at 16, 17. S.E.B. was discharged from CCMC on November 27, 1996, and was scheduled to follow up with neurosurgery and ophthalmology. Pet. Ex. 6 at 4-5.

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[6] Cephalopelvic disproportion refers to the relationship of the fetal head to the maternal pelvis. *Dorland's* at 330.

[7] Macrocephaly refers to an "unusually large size of the head." *Dorland's* at 1092.

[8] Hydrocephalus ex vacuo is a "compensatory replacement by cerebrospinal fluid of the volume of tissue lost in atrophy of the brain." *Dorland's* at 878.

[9] "IgM" refers to immunoglobulin M, a glycoprotein that functions as an antibody. *Dorland's* at 919.

[10] During the entitlement hearing, Petitioners' expert, Dr. Bellanti, noted that S.E.B.'s IgM was "was 8, and the normal range is 5 to 25." Tr. at 54.

[11] "IgG" refers to immunoglobulin G, a glycoprotein that functions as an antibody. *Dorland's* at 919.

On December 9, 1996, S.E.B. was evaluated by her pediatrician, Dr. Johnny Peeples, at Eastman Pediatric Clinic ("Eastman"). Pet. Ex. 10 at 38. No abnormalities were noted, though Dr. Peeples observed that S.E.B. had a slightly large and elongated head. *Id.* When S.E.B. saw Dr. Peeples again on January 29, 1997, Dr. Peeples again noted no abnormalities except that S.E.B. had a slightly bulging fontanel. *Id.* at 36.

In approximately mid-March 1997, S.E.B. began having "episodes of jerking and clonic movements three times a day, followed by being tired and sleepy." Pet. Ex. 8 at 125. At a visit with Dr. Peeples on April 10, 1997, Ms. Sumner reported that she "noticed some spells when [S.E.B.] turns off to the side for about a second at a time for about 15 times in a row," and that she was concerned that S.E.B. was having seizures. Pet. Ex. 10 at 36. Dr. Peeples noted that she "has an appointment with Dr. Smithson with in [sic] the next week," and "[w]e will probably get an EEG." *Id.*[12]

In early May of 1997, S.E.B. began to have episodes of "severe and prolonged jerks" with "eyes shifting back and forth lasting for 5-10 minutes." Pet. Ex. 8 at 125. Ms. Sumner brought S.E.B. to the Medical College of Georgia ("MCG") on May 12, 1997, where she reported that S.E.B.'s seizures had become more severe and prolonged "three to four days" prior. *Id.* at 125-26. S.E.B. was admitted "for hydrocephalus and to rule out tumor." *Id.*

On May 12, 1997, while at MCG, S.E.B. underwent a magnetic resonance imaging ("MRI") without contrast, a CT, and an electroencephalogram ("EEG") of her brain, which showed agenesis or partial agenesis of the corpus callosum,[13] at least one interhemispheric cyst, and compensatory dilation of both occipital horns, among other things.[14] Pet. Ex. 8 at 57, 126, 140-41; 143. There was no evidence of a brain tumor. *Id.* at 125. A retinal exam after dilation showed "whate [sic] areas around each disc with sharp borders, consistent with the lesion seen in Aicardi syndrome." *Id.* at 125. Upon discharge from MCG on May 14, 1997, S.E.B. was diagnosed with infantile spasms, brain malformation, bilateral otitis media, developmental delay, diaper rash, and AS. *Id.* at 125. S.E.B. was started on Phenobarbital and Adrenocorticotropic hormone injection treatment, which ultimately decreased the frequency and severity of the seizures. *Id.* at 126; *see also id.* at 51.

After discharge, S.E.B. continued to treat at MCG. On July 1, 1997, neurosurgeon Anne Marie Flannery noted that there had been "[n]o seizures since discharge on 5/12/97."

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[12] The records do not reflect that S.E.B. actually underwent an E.E.G. in April of 1997.

[13] Callosal agenesis is "a defect of the callosal structures (corpus callosum) of the brain." *Dorland's* at 37.

[14] The MRI showed agenesis of the corpus callosum and two interhemispheric cysts; the CT showed partial agenesis of the corpus callosum and one interhemispheric cyst.

Pet. Ex. 8 at 50-51. Pediatric ophthalmologist Steven Brooks noted upon examination that, although "[t]he anterior segment of each eye was normal[,] … the funduscopic examination did show characteristic fundus lesions of Aicardi's [sic] syndrome. Specifically, there were numerous 'punched-out' lacuner-type [sic] lesions throughout both fundae." *Id.* at 45. Dr. Brooks noted that his "colleague, Dr. Dennis Marcus, whom [sic] specializes in retina, also had a look at the left fundus but felt that the pigmentation overlying the nerve was … consistent with the Aicardi's [sic] syndrome." *Id.*

As of October 7, 1997, MCG neurologist James Carroll noted that S.E.B. had AS and that she continued to have "about 10 sets of spasm-like episodes per day." Pet. Ex. 8 at 38-39. On December 3, 1997, MCG pediatric neurologist Patricia Hartlage noted that S.E.B. had "responded somewhat to ACTH [Adrenocorticotropic hormone], although she still had as many as ten mild clusters a day until recently." Pet Ex. 8 at 36. During another visit with S.E.B. on October 6, 1998, when S.E.B. was almost two years old, Dr. Hartlage noted that S.E.B. "ha[d] a history of AICARDI syndrome and infantile spasms. She is cruising but is not walking independently. Her verbal development is a little more advanced than her gross motor skills, with perhaps 10 words, a good listening vocabulary, good social interaction, and a sense of humor." Pet. Ex. 8 at 35 ("Aicardi" capitalized in original).

On December 11, 1998, S.E.B. was re-admitted to MCG for placement of a Ventriculoperitoneal shunt, in order to relieve intraventricular pressure. Pet. Ex. 8 at 74-91. Post-surgery, S.E.B. was noted to be "more alert" and "more verbal." *Id.* at 25. On January 12, 1999 and August 24, 1999, S.E.B. was again noted to have been "doing well." *Id.* at 8-9, 19-21.

On January 10, 2001, S.E.B. was seen at Eastman for a fever. Pet. Ex. 10 at 26. Records indicate that "she was recently seen at the ER for a breakthrough seizure." *Id*. The assessment at Eastman was acute viral syndrome and AS with seizure disorder. *Id*. On August 15, 2002, S.E.B. was taken by ambulance to Dodge County Hospital in Eastman, Georgia because she was having seizures. Pet. Ex. 11 at 78. Her treating physician prescribed an increase in Phenobarbital. *Id.* at 75.

On April 22, 2004, S.E.B. was seen at Houston Neurology in Warner Robins, Georgia. Pet. Ex. 10 at 79. Notes from the exam indicate that S.E.B. had been fairly stable since her last visit. *Id.* S.E.B. had been taking 120 mg of Phenobarbital a day and 500 mg of Lamictal twice a day. *Id.* S.E.B.'s condition further stabilized, and at a follow-up appointment on July 29, 2004, she was having only two or three brief seizures a week. Pet. Ex. 10 at 78. Her treating neurologist, Abdul Qadir, recommended decreasing her Phenobarbital to 105mg a day in divided dosages. *Id.*

S.E.B. returned to Houston Neurology again on February 3, 2005. Pet. Ex. 10 at 77. Her mother complained that she had periods of "behavioral outbursts" and questioned whether her shunt was working properly. *Id.* During the exam, S.E.B. was uncooperative and had poor eye contact. *Id.* A CT scan was recommended, and her prescribed

Phenobarbital dosage was decreased due to infrequent seizures (occurring only once every two weeks). *Id*. The CT scan results from March 7, 2005 showed hydrocephalus ("more pronounced on the left side") and indicated that the shunt tube may not be working. Pet. Ex. 10 at 45.

S.E.B. was seen at the Children's Neurology Center of Macon on April 6, 2006. Pet. Ex. 10 at 71. Her EEG results from January 2006 were described as "profoundly abnormal" and she was noted to be symptomatic of secondary generalized epilepsy syndrome. *Id.* Other medical impressions were AS, West's Syndrome, Mental Retardation, Cerebral Palsy, and possible Lennox-Gastaut Syndrome.[15] *Id.* Her seizures were poorly controlled and she was resistant to medication. *Id*. At a follow-up visit to the Children's Neurology Center of Macon on August 28, 2007, she was prescribed an increase in her Lamictal to 200mg twice a day. Pet. Ex. 10 at 69-70.

On April 30, 2008, S.E.B. was noted to be stable and her medication was "tolerated well." Pet. Ex. 10 at 66. The working impression of S.E.B.'s condition was "Lennox-Gastaut Syndrome with a history of pharmacoresistant epilepsy." *Id.* at 67. S.E.B. returned to the Children's Neurology Center on September 30, 2008, where notes indicate that she had "a remarkable reduction in the frequency of breakthrough seizures" on the medication Topamax.[16] *Id.* at 62.

On February 15, 2010, an EEG resulted in "findings consistent with a diffuse underlying disturbance of neuronal function with superimposed interictal features of a secondary generalized epilepsy such as that can be seen in Lennox-Gastaut syndrome." Pet. Ex. 9 at 17.

S.E.B. was seen at East Texas Medical Center in Tyler, Texas on June 21, 2012. Pet. Ex. 15 at 9. The physician's assessment was that S.E.B.'s diagnoses included AS and chronic seizure disorder (now only on one medication). *Id*. The physician also noted that S.E.B. was having an increasing amount of interaction with family members and more difficulty with discipline. *Id.* At her follow-up visit on August 16, 2012, she was reportedly still having seizures, as well as daily partial spells. Pet. Ex. 15 at 10. She was also having grand mal seizures during her menstrual period. *Id.* Notes indicate that an increase in her anticonvulsant medication, Banzel, to three a day, appeared to decrease the number of generalized seizures. *Id.*

The most recent medical record available is from a May 13, 2013 neurological follow-up. Pet. Ex. 15 at 13-14. At that time, S.E.B. she was noted to have mental retardation, AS, and frequent seizures. *Id*. Her medications included Depo-Provera and Banzel. *Id.*

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[15] Lennox-Gastaut syndrome is "an atypical form of absence epilepsy characterized by diffuse slow spike waves, often with atonic, tonic, or clonic seizures and mental retardation; there may also be other neurological abnormalities or multiple seizure types. Unlike typical absence epilepsy, it may persist into adulthood." *Dorland's* at 1837.

[16] Records documenting when this medication was prescribed are absent.

II. Procedural Overview

The procedural history of this case is straightforward but protracted. Petitioners filed this vaccine petition on S.E.B.'s behalf on November 19, 1999, and the case was initially assigned to Special Master George Hastings. Medical records, including Exhibits 1 through 8, were filed between December 22, 1999 and March 21, 2000.

On April 18, 2000, Respondent filed a Rule 4 Report recommending against compensation in this case because, Respondent argued, Petitioners had not established by a preponderance of the evidence that S.E.B. suffered a vaccine-related injury. Resp. Report at 1-2. Respondent also took the position that, under 42 U.S.C. § 300aa-11(c)(1)(A), S.E.B. had not "received" a vaccine set forth in the Vaccine Injury Table, because the vaccine had been administered to her pregnant mother. *Id.* at 5. Respondent subsequently moved for dismissal of the petition under § 300aa-11(c)(1)(A). *See* Motion to Dismiss, July 13, 2000.

On February 8, 2001, Special Master Hastings ruled that Petitioners' stated legal theory was "untenable," *see Burch v. Sec'y of Health & Human Servs.*, 99-946V, 2001 WL 180129 (Fed. Cl. Spec. Mstr. Feb. 8, 2001), but subsequently held the case "in abeyance for an indefinite period, in light of currently ongoing efforts to amend the Vaccine Act, amendments which might affect petitioner's burden in this proceeding." Order, March 29, 2001.

Six years later, Special Master Hastings issued an order directing Petitioners to file a status report indicating whether they desired to continue with the proceedings that were held in abeyance or whether another course of action was favored. Order, May 14, 2007. Petitioners requested and were given an opportunity to re-brief the issue of whether S.E.B. is eligible for a Program award based on the immunization administered to her mother while pregnant. Status Report, June 27, 2007; Order, July 16, 2007. Petitioners filed their brief on October 22, 2008, Respondent filed her brief on December 22, 2008, and Petitioners filed a Reply on February 24, 2009.

On April 9, 2010, Special Master Hastings concluded, in light of intervening United States Supreme Court opinions, that Petitioners *would* qualify for a Program award if they could prove, as a factual matter, that S.E.B.'s injuries were caused by the MMR vaccine. *Burch v. Sec'y of Health & Human Servs.*, 99-946V, 2010 WL 1676767, at *2-3 (Fed. Cl. Spec. Mstr. Apr. 9, 2010). In other words, although Master Hastings held as a *legal matter* that S.E.B. could "receive" the vaccine as a result of the administration of the vaccine to Shon while she was pregnant with S.E.B., he did not to rule on the *factual matter* of whether such receipt actually occurred. *See generally id.* at *7-8. Rather, Special Master Hastings held, "[i]n light of my legal ruling above, the petitioners should determine whether they can obtain an expert report opining (1) that the vaccine likely proceeded through [Ms. Sumner]'s system into the system of the *in utero* [S.E.B.], *and* (2) that the vaccine likely caused injury to [S.E.B.]." *Id*. at *13 (emphasis in original). Petitioners were to file an expert report in compliance with Special Master Hastings' Order "as soon as possible;" in the event that "no such report [was] filed in 60 days, the petitioners … [were to file] status reports at 60-day intervals … until such an expert report is filed." *Id.* at *10.

Between June 8, 2010 and October 7, 2011, Petitioners filed nine status reports.[17] In each status report, Petitioners reported that they had not obtained an expert report because they were in need of some missing medical records for S.E.B. When, by the fall of 2011, Petitioners still had not filed an expert report, Special Master Hastings issued the following Order: "Due to the age of this case, petitioners' counsel is hereby instructed to GIVE THIS CASE URGENT PRIORITY IN OBTAINING MEDICAL RECORDS. In the next status report, if all records have not been obtained, counsel shall explain in detail why not." Order, October 25, 2011, at 1 (capitalized in original). Petitioners ultimately filed the outstanding medical records on November 17, 2011. *See* Pet. Ex. 9-11.

Special Master Hastings subsequently directed Petitioners to file status reports every 30 days until an expert report had been filed. Order, December 14, 2011, at 1. After Petitioners had filed four more status reports,[18] Special Master Hastings warned Petitioners "that if they cannot file an expert report within six months of the date of this Order, I will dismiss the petition for failure to prove the case." Order, April 16, 2012, at 1.

Petitioners ultimately filed their first expert report, authored by Dr. Joseph Bellanti, on October 9, 2012. *See* Pet. Ex. 12. Petitioners later filed two supplemental expert reports, also authored by Dr. Bellanti, on September 10, 2013 and November 8, 2013.[19] *See* Pet. Ex. 16, 27.[20] Respondent, in turn, filed two expert reports from Dr. Gerald Raymond on May 30, 2013 and September 26, 2013.[21] *See* Resp. Ex. A, C.

An entitlement hearing was held in Washington, D.C., on November 22, 2013. Both parties' experts testified. Although the parties ultimately agreed that S.E.B.'s signs and symptoms are consistent with Aicardi syndrome, they disagreed as to the etiology of S.E.B.'s Aicardi syndrome. Tr. at 28, 64-65. Dr. Bellanti took the position that a partial rubella infection can cause an injury with the same signs and symptoms as Aicardi syndrome and that, in this instance, the rubella vaccine caused such an infection in S.E.B.'s pregnant mother, that

[17] Petitioners filed status reports on June 8, 2010; August 9, 2010; October 8, 2010; December 7, 2010; February 7, 2011; April 8, 2011; June 7, 2011; August 8, 2011; and October 7, 2011.

[18] Petitioners filed status reports on February 13, 2012; March 14, 2012; March 19, 2012; and April 12, 2012.

[19] This case was assigned to the undersigned in the interim, on April 19, 2013.

[20] Petitioners initially labeled Dr. Bellanti's September 10, 2013 and November 8, 2013 expert reports both as Exhibit 16. On November 21, 2013, Petitioners filed a corrected exhibit list which re-labeled the November 8, 2013 report as Exhibit 27.

[21] Dr. Raymond's supplemental report appears to have been incorrectly dated September 23, 2012. Resp. Ex. C. The report was likely signed on September 23, 2013. *See* Pet. Ex. 16.

the infection crossed the placenta, and that it infected *in utero* S.E.B. Tr. at 20-23, 65. Dr. Raymond agreed that Aicardi syndrome is the correct diagnosis for S.E.B., but argued that congenital rubella syndrome ("CRS")[22] is not the likely etiology of her symptoms. Tr. at 111-12. According to Dr. Raymond, Aicardi syndrome and CRS are entities that describe two different sets of signs and symptoms, and the signs and symptoms that define the two syndromes essentially do not overlap. Tr. at 120-21.

After the hearing, Petitioners and Respondent filed several additional articles, some of which had been discussed at the hearing. *See* Pet. Exs. 34, 35, 36; Resp. Exs. D, E. One of the articles filed after the hearing was Petitioners' Exhibit 35, the translation of Petitioners' Exhibit 28, which the undersigned had admitted at hearing over Respondent's objection. *See infra* note 30; tr. at 24-32. Respondent filed a second supplemental expert report, authored by Dr. Raymond, in response to the new medical literature that had been filed. *See* Resp. Ex. F. This matter is now ripe for a ruling.

III. Analysis

A. Standards of Adjudication

To receive compensation under the Vaccine Act, Petitioners must demonstrate either that: (1) S.E.B suffered a "Table injury" by receiving a covered vaccine and subsequently developing a listed injury within the time frame prescribed by the Vaccine Injury Table set forth at 42 U.S.C. § 300aa-14, as amended by 42 C.F.R. § 100.3; or (2) S.E.B. suffered an "off-Table Injury," one not listed on the Table as a result of her receipt of a covered vaccine. *See* 42 U.S.C. §§ 300aa-11(c)(1)(C)(ii)(I); *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1321-22 (Fed. Cir. 2010); *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1320 (Fed. Cir. 2006).

Because Petitioners do not allege a Table injury in this case, they must prove that S.E.B.'s injury was caused-in-fact by a covered vaccine. To establish causation-in-fact, Petitioners must demonstrate by a preponderance of the evidence that the vaccine was the cause of the injury. § 300aa-13(a)(1)(A). Petitioners are required to prove 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 1321-22 (quoting *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)).

In *Althen v. Secretary of the Department of Health and Human Services*, the Federal Circuit set forth a three-pronged test used to determine whether a petitioner has established a

[22] Congenital rubella syndrome is defined as "developmental abnormalities resulting from transplacental infection of the fetus with rubella, usually in the first trimester of pregnancy; maternal infection may be subclinical. The anomalies may include cardiac lesions, ocular lesions, deafness, microcephaly, mental retardation, and generalized growth retardation, sometimes associated with acute self-limited conditions such as thrombocytopenic purpura, anemia, hepatitis, encephalitis, and radiolucencies of long bones. Infected infants may shed virus to all contacts for an extended period." *Dorland's* at 1826.

causal link between a vaccine and the claimed injury. 418 F.3d 1274, 1279 (Fed. Cir. 2005). The *Althen* test requires the petitioners to set forth: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id.* To establish entitlement to compensation under the Program, a petitioner is required to establish each of the three prongs of *Althen* by a preponderance of the evidence. *Id.*

1. *Althen* Prong 1.

Under the first prong of *Althen*, Petitioners must offer a scientific or medical theory that explains how the relevant vaccine could have caused S.E.B.'s alleged injury. *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1375 (Fed. Cir. 2009); *Pafford v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1355-56 (Fed. Cir. 2006). Petitioners' theory of causation must be informed by a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994) (citing *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992)); *see also Veryzer v. Sec'y of Health & Human Servs.*, 98 Fed. Cl. 214, 222-24 (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").

Vaccine Rule 8(b)(1) provides, in part, that the special master "must consider all relevant and *reliable* evidence governed by principles of fundamental fairness to both parties." *Id*. Emphasis added. The seminal case on what constitutes reliable evidence in the scientific context is *Daubert v. Merrell Dow Pharmaceutical, Inc.*, 509 U.S. 579 (1993). In *Daubert*, the Court held that "in order to qualify as 'scientific knowledge,' an inference or assertion must be derived by the scientific method. Proposed testimony must be supported by appropriate validation—*i.e*., 'good grounds,' based on what is known." *Id.* at 590. The application of *Daubert* principles in Program cases has been approved repeatedly by the Federal Circuit. *See, e.g., Cedillo v. Sec'y of Health & Human Servs.*, 617 F.3d 1328, 1338-39 (Fed. Cir. 2010) ("We have previously held that Special Masters may look to the *Daubert* standards in evaluating expert testimony.") (footnote omitted); *Terran v. Sec'y of Health & Human Servs.,* 195 F.3d 1302, 1316 (Fed. Cir. 1999) (holding that it is appropriate for Special Masters to utilize *Daubert* as a framework for evaluating reliability of causation-in-fact theories presented in Program cases).

Daubert makes clear that no single factor or even group of factors constitutes a litmus test for the reliability of scientific evidence. *Daubert*, 509 U.S. at 594-95. *See also Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 151 (1999) (the *Daubert* "list of factors was meant to be helpful, not definitive."). That does not mean, however, that scientific evidence should be admitted and evaluated in legal proceedings without regard to its reliability. Rather, the factors considered when evaluating reliability are intended to be flexible and to fit the particular case and kind of evidence involved. *See Daubert*, 509 U.S. at 594-95 (1993) (holding that "[t]he inquiry envisioned … [is] a flexible one. Its overarching subject is the scientific validity and thus the evidentiary relevance and reliability – of the principles that underlie a proposed

submission. The focus, of course, must be solely on principles and methodology, not on the conclusions that they generate.")

If a petitioner relies on a medical opinion to support her theory, Special Masters must consider the basis for the opinion, and the reliability of that basis, in determining how much weight to afford the proffered 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.") (citing *Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1361 (Fed. Cir. 2000)). When evaluating the reliability of an expert's opinion, special masters must ascertain whether the information upon which the expert is relying is accurate, because inaccuracies in the expert's factual assumptions compromise the reliability of the view offered. *See Perreira v. Sec'y of Health & Human Servs.*, 33 F.3d 1375, 1376-77 (Fed. Cir. 1994) (an expert opinion is no better than the soundness of the reasons supporting it). The persuasiveness of the expert's testimony must be evaluated, and the testimony of one side's expert may be rejected when there is a reasonable basis for doing so. *Burns v. Sec'y of Health & Human Servs.*, 3 F.3d 415, 417 (Fed. Cir. 1993).

2. *Althen* Prong 2.

In addition to showing that the vaccine at issue can cause a particular injury, a petitioner must also prove that the vaccine actually *did* cause the alleged injury in a particular case. *Althen*, 418 F.3d at 1279; *see also Pafford v. Sec'y of Health & Human Servs.*, No. 01-165V, 2004 WL 1717359 at *4 (Fed. Cl. Spec. Mstr. July 16, 2004). 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. *See, e.g., Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1375-77 (Fed. Cir. 2009); *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1326 (Fed. Cir. 2006); *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). "Petitioner must show that the vaccine was the 'but for' cause of the harm … or in other words, that the vaccine was the 'reason for the injury.'" *Pafford v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1356 (Fed. Cir. 2006) (internal citation omitted). A petitioner does not meet this obligation by showing a temporal association between the vaccination and the injury; the petitioner must explain how and why the injury occurred. *Id*.

A petitioner need not make a specific type of evidentiary showing, i.e., the petitioner is not required to offer "epidemiologic studies, rechallenge, the presence of pathological markers or genetic predisposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." *Cappizano*, 440 F.3d at 1325. Instead, a petitioner may satisfy her burden by presenting circumstantial evidence and reliable medical opinions. *See id.* at 1325-26.

3. *Althen* Prong 3.

The third *Althen* prong requires a petitioner to establish a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1278-81. This term has been equated to the phrase "medically-acceptable temporal relationship." *Id*. at 1281. The petitioner must present "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-in-fact." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008).

A petitioner's *Althen* Prong 3 theory must coincide with her theory as to how the relevant vaccine can cause the alleged injury under Prong 1. *de Bazan*, 539 F.3d at 1354. A Special Master cannot infer causation from temporal proximity alone. In fact, where a petitioner's expert views the temporal relationship as the "key" indicator of causation, the claim must fail. *See Thibaudeau v. Sec'y of Health & Human Servs.*, 24 Cl. Ct. 400, 403-04 (Fed. Cl. Oct. 23, 1991); *see generally Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992); *Hasler v. United States*, 718 F.2d 202, 205 (6th Cir. 1983).

B. The Experts' Qualifications

a. Dr. Bellanti's Qualifications

Dr. Joseph Bellanti attended medical school at The University of Buffalo School of Medicine in 1958 and completed his residency in pediatrics at the Children's Hospital of Buffalo in 1961. Pet. Ex. 13 at 3. He was board-certified in pediatrics and by the conjoint board of Allergy and Immunology in 1964 and 1974, respectively. Pet. Ex. 13 at 4; tr. at 11. At the time of the entitlement hearing, Dr. Bellanti was a professor of pediatrics, microbiology, and immunology, and the Director of the International Center for Interdisciplinary Studies of Immunology at the Georgetown University School of Medicine, where he had joined the faculty in 1963. Pet. Ex. 13 at 1, 3; tr. at 10.

Dr. Bellanti testified that he has published over 400 peer-reviewed articles and over 20 books or book chapters, including a textbook in immunology (the fourth edition of which was published in 2012). Tr. at 10; Pet. Ex 13 at 12-41. He has been the president of several scientific organizations, including the Society for Pediatric Research, the American Association of Clinical Immunologists, and the American College of Allergy and Immunology. Tr. at 11; Pet. Ex. 13 at 5-7. He has served as editor-in-chief of several journals related to the study of pediatrics and immunology. Pet. Ex. 13 at 6; tr. at 11.

Dr. Bellanti also testified that he has a variety of experience specifically relevant to the issues in this case. He received post-doctoral training in developmental immunology at the University of Florida, where he studied the immune responses of young infants. Pet. Ex. 13 at 3; tr. at 10-12. He and his colleagues were "among the first to show the predominance of the IgM response in either infection or immunization in the newborn and in the fetus." Tr. at 11-12. While a research virologist at the Walter Reed Army Institute of Research between 1962

and 1964, he studied a group of infants infected with CRS and isolated the rubella virus for the first time from several bodily organs. Pet. Ex. 13 at 3; tr. at 12. Dr. Bellanti and his fellow researchers "were the first to describe the IgM as the predominant antibody following intrauterine infection." Tr. at 12; Pet. Ex. 17.[23] Also at Walter Reed, and at Georgetown University School of Medicine, Dr. Bellanti "performed studies of the sequential appearance of humoral antibody of the sequence of IgM followed by IgG, either following natural infection or following immunization with a variety of vaccines." Tr. at 13. He assisted with the development of an intra-nasal measles vaccine for infants and children, and he has written several articles about the adverse effects of the measles vaccine. Tr. at 14.

Based on the above qualifications, the undersigned admitted Dr. Bellanti as an expert in pediatrics, infectious diseases, immunology, and vaccines. Tr. at 12-13, 16.

Dr. Bellanti testified that he was "familiar with" the field of genetics, having done post-doctoral training and taken courses in the area. Tr. at 49. He also testified that he regularly diagnosed genetic conditions. Tr. at 50. However, Dr. Bellanti testified, he does not consider himself an expert in genetics. *Id.*

b. Dr. Raymond's Qualifications

Dr. Gerald Raymond attended medical school at the University of Connecticut before completing two years of pediatric residency at Johns Hopkins Hospital and four years of additional residency training in neurology, with special qualifications in child neurology, at Massachusetts General Hospital and abroad. Resp. Ex. B at 1; tr. at 106. After his residency training, Dr. Raymond did fellowships in developmental neuropathology and in genetics and teratology. Resp. Ex. B at 1; tr. at 107. At the time of the entitlement hearing, Dr. Raymond was a neurology professor at the University of Minnesota and the Director of Pediatric Neurology at the University of Minnesota Medical Center. Resp. Ex. B at 1; tr. at 107. He is board-certified in neurology, with special qualifications in child neurology, and in clinical genetics. Tr. at 108.

Dr. Raymond has "a standard pediatric neurology outpatient practice" in which he regularly diagnoses and treats patients with genetic and neurological disorders. Tr. at 108. He also sees patients "who have and who we evaluate for teratogenic effects."[24] Tr. at 109. He is a peer reviewer for a number of journals, and has published work in the agents that cause birth defects. Resp. Ex. B at 2-7, 9-11; tr. at 109-10.

The undersigned admitted Dr. Raymond as an expert in pediatrics, neurology, and genetics. Tr. at 110.

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[23] Bellanti, J., et al., *Congenital Rubella: Clinicopathologic, Virologic, and Immunologic Studies*, Am. J. of Diseases of Children, 1965; 110:464-72 [hereinafter *Congenital Rubella*].

[24] Teratogenic means "tending to produce congenital abnormalities." *Dorland's* at 1883.

C. The Parties' Arguments

a. Petitioners' Theory

1. Pathogenesis

Dr. Bellanti's theory, as expressed at the hearing,[25] is that the rubella vaccine crossed Ms. Sumner's placenta, infected the fetus, and caused a "partial" rubella infection in Ms. Sumner and S.E.B.[26] Tr. at 44-45 ("[T]he rubella vaccine given to the mother during the first trimester, causing the disease, is based upon the same mechanism that we see with the live natural virus, that it can replicate in the mother … infect the placenta, get into the fetus, and at the critical point .. cause these congenital defects"). Dr. Bellanti's theory regarding the "partial" infection was necessary to explain why S.E.B.'s symptoms are distinctly unlike those typically associated with CRS (which, purportedly, would only reflect the symptoms of a "full-blown" CRS infection). *See* Resp. Ex. E at 1-2 (identifying the primary and secondary symptoms of CRS, as described by the World Health Organization: cataracts, congenital glaucoma, congenital heart disease, loss of hearing, pigmentary retinopathy, purpura, splenomegaly, microcephaly, mental retardation, meningoencephalitis, radiolucent bone disease, and jaundice within the first 24 hours).

Generally speaking, Dr. Bellanti defined CRS as

> an entity caused by infection during pregnancy in the first trimester of pregnancy where the mother contracts a disease, rubella, German measles, the virus replicates in the respiratory tract, enters the blood, goes through the placenta and then to the fetus. And during that critical period of development in the first trimester, the replication of [the] rubella virus interferes with the development of many organ systems.

Tr. at 20-21. Unlike "classic" CRS (which enters the upper respiratory tract, replicates, and enters the bloodstream), CRS acquired by injection "goes directly into the tissues of the blood." Tr. at 85-86. Once in Ms. Sumner's bloodstream, Dr. Bellanti argued, the rubella virus – which, in a vaccine, is in its attenuated form[27] (i.e., it is "tame[d] … down so that it can induce

[25] Dr. Bellanti clarified significant aspects of his theory of the case, as articulated in his first three expert reports, during the entitlement hearing. *See* tr. at 66-75. To address the substantive merits of Petitioners' causation theory, the undersigned will rely primarily on Dr. Bellanti's hearing testimony as the most recent iteration of Petitioners' theory of the case.

[26] At the hearing, Petitioners clarified they are not alleging that the measles or mumps elements of the MMR vaccine were causally related to S.E.B.'s injury. *See* tr. at 52 ("[Petitioners are] not claiming measles virus or the mumps virus are involved; we're claiming rubella.").

[27] Attenuation is a "reduction in virulence of a pathogenic organism, usually by adaptation to another host or a different culture medium." *Dorland's* at 178.

a protective immune response, but [can't] produce an infection") – became virulent. Tr. at 34, 45. The process by which an attenuated virus converts to a virulent one is called "reversion." Tr. at 43. Dr. Bellanti described reversion as the "turning back or genetically being modified so that the genes that keep it in the attenuated state are modified back to a sequence … commensurate with the natural virus." Tr. at 43. The reverted, virulent virus, explained Dr. Bellanti, is now pathogenic[28] and, in the case of congenital rubella, teratogenic.[29] *Id.*

In an exhibit that was discussed during the hearing and filed post-hearing, Petitioners provided a case report of a "fatal case of the encephalitis associated with measles-rubella (MR) vaccine." Pet. Ex. 34 at 1.[30] A 31-year-old man, "previously in good health," developed "flu-like" symptoms three days after vaccination. *Id.* "Histopathology confirmed encephalitis and immunohistochemistry was positive for [rubella virus] on brain tissue. [Rubella virus] was also detected by qPCR and virus isolation in cerebrospinal fluid, brain and other clinical samples. The sequence obtained from the isolated virus was identical to that of the … vaccine strain." *Id.*[31]

Once the reversion had taken place in Ms. Sumner's body, Dr. Bellanti testified, the virulent (also known as "wild-type"[32]) virus "crossed the placenta, infected the fetus and caused the damage that gave the symptoms of Aicardi syndrome." Tr. at 48. Ms. Sumner need not have had symptoms in order for this infection to have occurred. Tr. at 84. This is called a

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[28] Pathogenic means "causing disease or morbid symptoms." *Dorland's* at 1396.

[29] It is unclear to the undersigned whether Dr. Bellanti's theory is that the infection caused the alleged injury by causing a genetic mutation or whether, alternatively, the infection caused the injury by inflicting teratologic damage on the developing fetus. One interpretation of Petitioners' argument is that environmental factors – i.e., a partial congenital rubella infection from a reverted rubella vaccine that crossed the placenta – caused one of S.E.B.'s X chromosomes to mutate. Another interpretation of Petitioners' argument is that the rubella virus, having reverted and crossed the placenta, caused teratological damage to the developing fetus, causing injuries that later manifested as Aicardi. The undersigned analyzes both of these theories in Section (D)(a)(2), *infra*.

[30] Gualberto, F., et al., *Fulminant encephalitis associated with a vaccine strain of rubella virus*, J. Clin. Virology, 2013; 1-4 [hereinafter *Gualberto*].

[31] In his second supplemental expert report, Dr. Raymond noted that the authors of this article "do not explain why this conversion to a wildtype infection would result in a severe, lethal disorder." Resp. Ex. F at 1. Dr. Raymond also noted that the authors do not discuss whether this was an isolated event or an issue with manufacture. *Id.* The patient did not have immunologic evidence of an acute reaction to rubella virus. *Id.*

[32] Wild type is defined as "the typical form occurring in a natural population or in the standard laboratory stock, as a strain, phenotype, or gene, and therefore designated as representative of the group." *Dorland's* at 1993.

"sub-clinical" infection. *Id.* Once inside the placenta, the virus did not result in a "full-blown" infection that would later manifest as CRS; rather, Dr. Bellanti argued, the fetus developed a "partial" infection. Tr. at 59, 61, 85-86. Dr. Bellanti described the nature of a partial infection:

> [N]ot all cases of congenital rubella give you the full-blown picture. You can have variations of it, depending on which virus is infecting the fetus …. What we're talking about in this case is exposure to an attenuated virus vaccine that's administered via the parental route, not the respiratory route, and which, presumably, reverted back to virulence and infected the baby.

Id. "[T]he amount of virus …. [is] determined by the amount of viral replication in the placenta and in the baby;" only cases of full-blown infection will have the classic findings of "high IgM, the thymus, the eyes, the heart and so forth." Tr. at 86-87. The "damage [to the fetus] … is largely dependent upon the severity of the infection and also the stages of fetal development during which the fetus is infected." Tr. at 34, 45.

Moreover, Dr. Bellanti testified, a CRS infection can be variable both in terms of severity and in terms of clinical expression. Tr. at 22. Although the "classical presentation" of CRS involves "microcephaly, cataracts, heart disease, jaundice," "there are variations of it that can occur with one or two or three symptoms. All signs and symptoms don't have to be present." *Id.* A rubella infection can affect "any of the organs or tissues of the fetus." Tr. at 33; *see also* Pet. Ex. 33[33] ("Response of the fetus to rubella virus covers a wide range. The infection may cause no apparent damage, or it may result in single, mild to multiple, severe anomalies."). The damage caused by the virus is "largely dependent upon the severity of the infection and also the stages of fetal development during which the fetus is infected." Tr. at 45. "Rubella in fetal tissues has a propensity to persist throughout pregnancy," and its clinical expression depends on "the amount of viral replication, the stage at which [the] virus is entered, and the degree of virulence of the infecting virus." Tr. at 88.

The fact that Ms. Summer had been immunized with an MMR vaccine 18 years prior, *see* Pet. Ex. 1 at 2, would not have precluded the alleged pathogenesis, because of "the waning of immunity following immunization." Tr. at 45-46, 90-92.

According to Dr. Bellanti, a "hallmark of intrauterine or neonatal infection" is "a very prominent" immunoglobulin M ("IgM") in the bloodwork of a newborn. Tr. at 53. The degree of elevation in IgM "depends upon the degree of viral involvement, whether the immune system is infected and so forth. So, not all babies with – with congenital rubella syndrome have an elevated IgM." Tr. at 56. In a sample taken from S.E.B.'s cord blood, "the [total] IgM reported was 8, and the normal range is 5 to 25." Tr. at 54. Dr. Bellanti testified that the absence of IgM elevation doesn't exclude the possibility of a partial rubella infection. Tr. at 56. He also testified that a test for *specific* rubella IgM antibody, the results of which would

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[33] Horstmann, D., *Viral Infections in Pregnancy*, Yale J. of Biol. and Med., 1969; 42:99-112 [hereinafter *Horstmann*].

have permitted a conclusive diagnosis of rubella infection, was not performed on S.E.B. Tr. at 98-100.

Petitioners provided one article describing a case study of a newborn who displayed symptoms consistent with Aicardi syndrome, and for whom, according to the author, "a serologic diagnosis of [CRS] was made." Pet. Ex. 35 at 1.[34] The author does not refer to the results of any testing done on the mother, but she does note that the mother "did not recall having any rash or fever during the pregnancy." *Id.* There is no indication that the mother received any vaccines. The author indicates that the child had a rubella titer consistent with a rubella infection, but concedes that she was unable to "formally confirm the congenital rubella" because the child died at six months old. *Id.* at 2-3. It is unclear from the article how old the child was when the titers were drawn, but Dr. Bellanti testified at the hearing that there was "presumptive evidence" that the child suffered from CRS: upon testing, the baby's serum was susceptible to 2-mercaptoethanol, which may have constituted evidence of the presence of IgM antibodies. Tr. at 83-84; *see also* Pet. Ex. 36[35] (discussing the use of 2-mercaptoethanol to detect IgM).

2. Overlap of CRS and Aicardi syndrome

Dr. Bellanti explained that, despite its name, CRS is "not really a syndrome;" it is a disease. Tr. at 20-21. "The basic difference [between a "disease" and a "syndrome"] is [that] a disease is an entity with signs and symptoms where we know what the etiology is. We know the cause. A syndrome is a group of signs and symptoms where we don't know. There may be many causes." Tr. at 23. When the entity "CRS" was named, prior to 1964, researchers believed that the signs and symptoms were associated with a virus, but they did not know. Tr. at 23-24. The cause of CRS is now generally understood to be a full-blown rubella infection.

Petitioners ultimately conceded that S.E.B.'s signs and symptoms are consistent with Aicardi syndrome,[36] a diagnosis that is markedly different from CRS. *See* tr. at 23 ("the signs and symptoms of congenital rubella could be similar and could mimic the signs and symptoms of … Aicardi"), 28 ("[w]e're admitting that she fits the clinical diagnosis of Aicardi"). Aicardi syndrome has "no known genetic basis," Dr. Bellanti opined, and it is reasonable to believe that a partial rubella infection – a teratologic event – can cause it. Tr. at 20, 27. According to Dr.

[34] Orquin, J., *The Aicardi Syndrome: A Case Possibly Caused by Congenital Rubella*, Can. J. Ophthalmol., 1969; 16(4):200-02 (translated to English) [hereinafter *Orquin*]. The untranslated version of this article was filed as Pet. Ex. 28.

[35] Desmyter, J., et al., *The IgM Antibody Response in Rubella During Pregnancy*, J. Med. Microbiol., 1971; 4:107-14.

[36] At the hearing, Dr. Bellanti clarified that, in his First Supplemental Report, he had confused Aicardi syndrome and Aicardi-Goutieres syndrome. Tr. at 66-71. Dr. Bellanti ultimately agreed that S.E.B.'s signs and symptoms were consistent with Aicardi syndrome, not Aicardi-Goutiéres. *Id.*

Bellanti, "Aicardi syndrome is a collection of signs and symptoms caused by multiple etiologies, one of which is rubella infection." Tr. at 70.

Dr. Bellanti also conceded that the eye features and agenesis of the corpus callosum – both of which are present in S.E.B. – are almost always present in Aicardi, and are rarely, if ever, present in CRS. Tr. at 96. In addition, Dr. Bellanti agreed that the hallmarks of CRS – including cataracts, heart disease, hearing loss, and thrombocytopenic purpura – are not present in S.E.B.'s case, but he explained this in part by noting that CRS can infect any tissue in the body. Tr. at 21-22, 60-61. The fact that the rubella virus was introduced directly to Ms. Sumner's bloodstream, as opposed to through the respiratory tract, avoided some of Ms. Sumner's immunological system, and thereby "avoid[ed] some of the defense of the mother's immunological system and her ability to stop it going into the fetus through the placenta." Tr. at 44-45.

3. Rarity of Reversion

Dr. Bellanti agreed that it is rare for an attenuated virus to revert to a virulent virus – also known as a "wild" virus – but that it has happened before. Tr. at 34, 40-41, 96. He admitted that he has never encountered a case of a "vaccine virus, such as the type received by [Ms. Sumner], result[ing] in congenital rubella syndrome." Tr. at 62. According to the MMR vaccine package insert, of 700 pregnant women surveyed who received the rubella vaccine during pregnancy, none of the newborns had abnormalities consistent with CRS. Pet. Ex. 32 at 6; tr. at 62-64. According to the Centers for Disease Control and Prevention (CDC) Guidelines for Vaccinating Pregnant Women, of 226 pregnant women who received the MMR vaccine between 1971 and 1989, there were no reported cases of CRS. Pet. Ex. 25[37] at 4; tr. at 103-04. Even according to the medical literature submitted by Petitioners, "vaccination does not result in congenital abnormalities when inadvertently given in early pregnancy." Pet. Ex. 22 at 584.[38]

Dr. Bellanti explained that S.E.B.'s case is an extremely rare event, and that neither of the above surveys has studied large enough populations of pregnant women to be probative. Tr. 63-64. For ethical reasons, a larger study would be impossible, however. *Id.*

b. Respondent's Argument

Dr. Raymond agreed with Dr. Bellanti that "there is a theoretical risk to the fetus from vaccination of the mother during pregnancy with MMR," and that the MMR vaccine is contraindicated in pregnant women. Pet. Ex. 25 at 4; tr. at 103, 136-37. However, Dr. Raymond stated that there exists no epidemiologic evidence of a case of CRS "secondary to a pregnant individual receiving the MMR vaccine." Tr. at 112. Dr. Raymond agreed that the

[37] According to the CDC Guidelines, the MMR vaccine is contraindicated for pregnant women. U.S. Dept. of Health & Human Servs., Centers for Disease Control and Prevention, Guidelines for Vaccinating Pregnant Women, April 2013.

[38] Lee, J., et al., *Rubella Virus Replication and Links to Teratogenicity*, Clin. Microbiol. Rev., 2000; 13(4):571-87 [hereinafter *Lee*].

fact that the vaccine was administered to Ms. Sumner, rather than to S.E.B., has no bearing on whether it would regress to a wild virus. Tr. at 155. Dr. Raymond also agreed that it was possible, though rare, for a virus to convert to its virulent form. Tr. at 146-49. For instance, subacute sclerosing panencephalitis ("SSPE"), which is "an example of a case where the measles virus converts and then becomes virulent," occurs in about one in a million doses of the measles vaccine. *Id.* Dr. Raymond conceded that "a relatively minor [infection] in the mother … [could] still be a significant infection in the fetus." Tr. at 156. Depending on when the infection's viral load is spiking, a rubella infection may affect fetal development at different times of gestation. Tr. at 137-38.

Dr. Raymond testified that S.E.B. was tested for a broad IgM panel, but that a test specifically for IgM to rubella was not done; therefore, the blood testing results neither support nor refute Dr. Bellanti's theory. Tr. at 144. Similarly, although an IgG test was positive for rubella, this merely reflected that Ms. Sumner was immune, potentially as a result of her earlier MMR vaccination, and passed this immunity on to her child; it does not reflect that the child was infected with rubella *in utero*. Tr. at 145.

Dr. Raymond did not agree, however, that a rubella infection was the likely cause of S.E.B.'s injuries. Tr. at 113-14. Notwithstanding his testimony regarding the effects on a fetus of mild infections in the mother, Dr. Raymond opined that, specifically in the context of an attenuated rubella strain, "[i]f there was conversion to wildtype rubella, the mother should have been ill even if it was only a mild infection." Resp. Ex. F at 1.

Based on what is generally understood about the etiology of Aicardi syndrome, Dr. Raymond disagreed that infections are likely to play a role in causing it. There exists no epidemiologic evidence of a single case of CRS "secondary to a pregnant individual receiving the MMR vaccine." Tr. at 112. Aicardi syndrome is presumed to be caused by a dominant de novo mutation in an X-linked gene, and it generally occurs only in females (though it has been reported in rare instances in males with an extra X chromosome). Tr. at 113-15; Resp. Ex. A-1 at 3.[39]. *See also* Pet. Ex. 35 at 202; Pet. Ex. 30 at 4[40] ("the occurrence of the Aicardi syndrome only in females suggests an unproven genetic etiology"); Resp. Ex. A-1 at 2. It is presumed that Aicardi is caused by "a gene in the region of the X chromosome that undergoes something referred to as X inactivation." Resp. Ex. A-1 at 1, 4, 6. The gene itself has not been identified, but the existence of this genetic, chromosomal phenomenon is supported by sibling reports. *See* tr. at 115. According to Dr. Raymond, "there's really no doubt that this is a genetic disorder," and "it is not a disorder that has been associated with teratogenic effects." Tr. at 115. *See also Sutton* at 3 ("[a]t least six pairs of twins who are discordant for Aicardi syndrome are known, five of whom are confirmed dizygotic, excluding the possibility that the

[39] Sutton, V. and Van den Veyver, I.B., *Aicardi Syndrome,* http://www.ncbi.nlm.mh.gov /books/NBK1116 (2006) [hereinafter *Sutton*]. Respondent originally filed this article as Exhibit A-1; she later filed a duplicate as Exhibit C-1.

[40] Willis, J. and Rosman, N., *The Aicardi syndrome versus congenital infection: Diagnostic considerations*, J. Pediatr., 1980; 96(2): 235-39 [hereinafter *Willis*].

etiology is a prenatal toxin or other disruptive event"). Although some congenital deformities are thought to be associated with environmental influences *in utero*, such as cleft lip and palate, it has "never been shown to be the case" that a congenital infection can result in a genetic disorder. Tr. at 116, Resp. Ex. F at 2.

Dr. Raymond opined that, for the most part, the signs and symptoms that define each syndrome do not overlap. Aicardi syndrome is characterized by either partial or complete absence of the corpus callosum, distinctive lesions or "lacunae" of the retina of the eye, heterotopia,[41] and infantile spasms (a form of seizures). *See* Resp. Ex. A-1 at 2, 4. Frequently present are other types of brain defects which can be characteristic of the disorder, such as microcephaly, enlarged ventricles, or intracerebral cysts. Tr. at 113. Agenesis of the corpus callosum is a hallmark of Aicardi; it is rare in CRS. *See id*.; *see also Willis* at 4 ("Agenesis of the corpus callosum, another feature of the Aicardi syndrome, is not found in the infections, except in one doubtful case of congenital rubella.") The "salt and pepper" pigmented fundus that is characteristic of congenital rubella is distinctly unlike the fundus in the Aicardi syndrome. Tr. at 93-96; *see also Willis* at 4. And, rather than lacunar deformation of the eye, which is associated with Aicardi, a large number of people with rubella syndrome have "general cataract," which is not a feature of Aicardi. Tr. at 120.

In identifying the recommended surveillance standards for rubella and CRS, the World Health Organization ("WHO") recommends that serologic screening – that is, a blood test for rubella-specific IgM – be conducted in any case involving two primary symptoms or one primary symptom and one secondary symptom. Resp. Ex. E;[42] tr. at 118-20, 151-52. The primary symptoms, or "(a) symptoms," include cataracts, congenital glaucoma, congenital heart disease, loss of hearing, and pigmentary retinopathy; the secondary symptoms, or "(b) symptoms," include purpura, splenomegaly, microcephaly, mental retardation, meningoencephalitis, radiolucent bone disease, and jaundice within the first 24 hours. Resp. Ex. E at 1-2; tr. at 119. Dr. Raymond opined that S.E.B. has none of the (a) symptoms, and only one of the (b) symptoms: mental retardation. Tr. at 151-52.

Dr. Raymond explained that the signs and symptoms attributable to rubella infections and to Aicardi are different in kind because their etiologies are different. In general, Aicardi is a patchy abnormality consistent with X chromosome inactivation, *see* tr. at 113-14, and CRS,

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[41] Heterotopia have two types: 1) "an anomaly of the cerebral cortex in which a heterotopic band of grey matter is found between the lateral ventricles and the cortex," and 2) "a genetically heterogenous anomaly of the cerebral cortex in which nodular masses of grey matter line the walls of the ventricles and protrude in to [sic] the lumen." *Dorland's* at 856. Dr. Raymond described heterotopia as "neuronal migration, neurons … dividing along the ventricular walls, and then they migrate out to the cortex;" as a result, the neurons "don't form the proper connections," which "may be part of why children with Aicardi syndrome have such hard-to-control seizures." Tr. at 116-17.

[42] World Health Organization, *WHO-recommended surveillance standard of rubella and congenital rubella syndrome*, http://www.who.int/immunization/monitoring_surveillance /burden/vpd/surveillance_type/active/rubella_ standards/en/.

which is the result of an *in utero* infection that affects cell proliferation, produces a more diffuse abnormality. Tr. at 126-27. Rubella infections, in other words, reduce "the number of cells available," which explains the etiology of symptoms such as microcephaly and salt and pepper retinopathy. Tr. at 160. *See also* Pet. Ex. 22 at 584. Aicardi, in contrast, turns on inappropriate genes, resulting in the formation of a brain and/or a retina which, essentially, have holes in them. Tr. at 160. Accordingly, Dr. Raymond's opined, a child who had a rubella infection *in utero* "should … manifest congenital rubella syndrome and not an unrelated pattern of malformation." Resp. Ex. F at 1.

In response to *Orquin*, Dr. Raymond argued that the authors had failed to substantiate their claim that they had obtained serologic evidence of CRS in the studied newborn. Resp. Ex. F. Additionally, Dr. Raymond argued, the newborn's symptoms did not meet the WHO criteria for CRS. *Id*.; *see also* Resp. Ex. E.

D. Application of *Althen* to the Evidence

a. *Althen* Prong 1.

At the entitlement hearing, Dr. Bellanti conceded that his pre-hearing reports included some missteps, including asserting in his First Report that S.E.B.'s Aicardi syndrome was caused by the mumps component of the vaccine, tr. at 19, and confusing Aicardi syndrome with Aicardi-Goutières syndrome (AGS) in his First Supplemental Report. Tr. at 66-69; *see infra* Section (D)(a)(1)(iii). Petitioners affirmed at hearing that Petitioners' causation theory was focused solely on the rubella component of the vaccine, tr. at 52, that Aicardi syndrome, not Aicardi-Goutières syndrome, is the injury at issue in this case, tr. at 66-69, and that S.E.B.'s symptoms are consistent with the characteristics of Aicardi syndrome. Tr. at 28.

Mindful of the mandate that special masters "shall consider the entire record," 42 U.S.C. §300aa-13(b)(1); *see also Hines ex rel. Sevier v. Sec'y of the Dep't of Health & Human Servs.*, 940 F.2d 1518, 1528 (Fed. Cir. 1991), the undersigned has considered the experts' prehearing reports and exhibits both because they still provide relevant substantive information and because they are relevant to an assessment of the experts' credibility and the reliability of their overall scientific methodology. *See Porter v. Sec'y of Health & Human Servs.*, 663 F.3d 1242, 1250-51 (Fed. Cir. 2010) citing *Moberly*, 592 F.3d 1315, 1326 (holding that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act). That discussion follows in Section (D)(a)(1).

However, because Dr. Bellanti articulated a new theory of causation at the entitlement hearing, the undersigned has determined that it is appropriate to apply the *Althen* analysis primarily to Dr. Bellanti's hearing testimony as the most recent and complete iteration of Petitioners' theory of the case. That discussion is the focus of Section (D)(a)(2).

1. Dr. Bellanti's expert reports and medical literature cast doubt on the reliability of his scientific methodology

In the present case, the reliability issues with Dr. Bellanti's reports and testimony are so myriad and pervasive that they cast doubt upon the reliability of his opinions. A detailed discussion of several of the more problematic issues follows.

i. Reliance on evidence not available to all parties; late disclosed articles; foreign language articles; theories presented for the first time at hearing

It is a basic tenet of due process and fundamental fairness that all parties to a proceeding should have an opportunity to review and evaluate all of the evidence upon which the decision in that proceeding may be based. In the vaccine context, where discovery is limited, *see generally* Vaccine Rule 7, this principle has been given effect in a number of ways, including full disclosure of medical records, early disclosure of expert opinions and the basis therefor, and post-hearing briefing where necessary. The findings of a special master will be overturned if they appear to be based on information the parties did not have an opportunity to address at hearing or in briefing. *Davis v. Sec'y of Health & Human Servs.*, 94 Fed. Cl. 53, 65-66 (2010); *Kirkpatrick v. Sec'y of Health & Human Servs.*, No. 90-877V, 1991 WL 242997, at *3 (Fed. Cl. Spec. Mstr. 1991). Advance notice of evidence and theories is particularly important in a highly scientific or technical context such as the Vaccine Program, where an adequate response to new information may require additional scientific research and evaluation.

This type of notice issue was particularly problematic in this case, as will be discussed in detail below.

I. Late Filed Exhibits; New Theories Presented for the First Time at Hearing

The undersigned understands that circumstances arise in vaccine cases that make the late filing of expert reports or exhibits necessary: The petitioner's diagnosis is in dispute, or her medical condition changes; the science in the field is changing rapidly, and new studies are being filed; petititioners have difficulties obtaining an expert. But no such circumstances applied in this case. S.E.B.'s Aicardi diagnosis had been consistent in the medical notes of treating physicians since she was an infant, and while there was a delay of almost two years while Petitioners obtained updated medical records, neither expert used those records in any substantive way in formulating his opinions. The questions of whether the vaccine could cross the placenta and cause injury, and whether the attenuated vaccine virus could revert to virulence, had been pending in the case from its filing, and at a minimum since Special Master Hastings' ruling on the vaccinee issue in 2010. And yet, *Horstmann*, published in 1969, Petitioners' intended answer to those questions, was not filed until November 20, 2013, two days before hearing. *See* Pet. Ex. 33. *Orquin* was published in 1981, and most of the literature upon which Petitioners relied had been published decades before the case went to hearing. *See* Pet. Ex. 28, 35. Dr. Bellanti filed his First Report in 2012, and yet he was still formulating his

theory concerning "partial" infection and "full-blown" versus "not full-blown" CRS as he was testifying at hearing.

There are no extenuating circumstances in this case, no reason for these late filings. The prejudice, the damage to the proceedings, to Respondent's ability to understand the literature and the theories and respond to them cogently, is obvious. Evidence submitted this late in proceedings, in the absence of extenuating circumstances, raises issues under the fundamental fairness provision of Vaccine Rule 8.

II. Use of an untranslated foreign language article

In his Second Supplemental Report, Dr. Bellanti quoted *Orquin* as saying:

> [t]his paper reports the first Canadian case of Aicardi's syndrome, consisting of septo-optique dysgenesis, with absence of the corpus callosum, hypsarrhythmia, multifocal lacunar choroiditis and minor vertebral anomalies, in a baby girl. For the first time in such a case a serologic diagnosis of congenital rubella was made.

Pet. Ex. 28 at 4. However, this is not actually a quote from the article itself. It is a two-sentence English-language summary of the article, the source of which is uncertain. The actual article is in French; it was attached to Dr. Bellanti's Second Supplemental Report and relied on at hearing without translation. Dr. Bellanti's Second Supplemental Report was filed November 8, 2013, fourteen days before hearing. In preparing for the hearing, it simply did not occur to the undersigned that experienced counsel and an experienced expert witness would rely on an untranslated article at hearing. Petitioners had not attempted to get a translation by the date of hearing, however, instead asserting that "Dr. Bellanti, I think, understands French fairly well and can probably interpret fairly well what is said there," Tr. at 24, to which Respondent, obviously, objected under Vaccine Rule 8.

This would have been a reliability issue even if *Orquin* was peripheral to Petitioners' claims, but it was not. *Orquin*, along with *Gualberto* (which was not submitted until the day of hearing), was the basis of Petitioners' argument that one of the etiologies of the constellation of symptoms that constitute Aicardi syndrome is congenital rubella infection. Tr. at 65-66; *see also* Pet. Ex. 34, 35. In addition, "what the serologic basis was for that [*Orquin*] diagnosis of congenital rubella," was also crucial. Tr. at 25, 81-84.

Orquin was published in 1981; the Aicardi diagnosis and whether it was caused by the MMR vaccine has been the issue since the petition was filed. There was no reason a translation could not have been available at, and before, hearing. The fact that it was not undermined the reliability of this specific argument, and further undermined the undersigned's confidence in Dr. Bellanti's expert opinion as a whole.

ii. Use of Outdated Literature

This significant reliability issue is exemplified by Petitioners use of *Horstmann*. *See* Pet. Ex. 33. This article was submitted for publication on August 15, 1969, and was published in the October 1969 volume of the Yale Journal of Biology and Medicine. *Id*. Petitioners cited it in response to Special Master Hastings' 2010 question concerning "whether the vaccine likely proceeded through Mrs. [Sumner]'s system into the system of an *in utero* S.E.B." Pet. Ex. 27 at 1; 2010 Ruling at 13. It was the only evidence submitted by Petitioners on the issue of whether the vaccine could have crossed the placenta. In addition, along with a single case report about vaccine reversion in an adult that was submitted on the day of hearing,[43] *Horstmann* was the only evidence even marginally relevant to the question of whether an attenuated virus can revert to virulence in a pregnant woman and injure a fetus *in utero*. *See* Pet. Ex. 27 at 1.

Horstmann was cited by Petitioners for this assertion: "Because all rubella vaccines contain live virus, *they are contraindicated in pregnancy*. This is particularly true since there is now evidence from trials in women scheduled for therapeutic abortion that the attenuated virus can infect the placenta, and probably the fetus." Pet. Ex. 33 at 9 (emphasis in original). The article documenting that "evidence from trials" was published in August 1969; it was filed as Respondent's Exhibit D. It included this summary:

> On the basis of the results reported here, it is not possible to draw definite conclusions concerning fetal infection by rubella vaccine virus. It should be noted, furthermore, that our studies to date concern only the HPV-77-DK12 vaccine.
>
> Inconclusive as they may be, the present results on fetal infection, added to the data concerning presence of vaccine virus in the blood, placenta, and uterine cervix, do reemphasize the need, at least until more data has been obtained, to observe proper precautions to avoid the inadvertent vaccination of pregnant women.

Resp. Ex. D at 4. These quotes point out the perils of relying on literature that is almost 45 years old. The first live attenuated vaccine, HPV-77, had been developed in 1966, only three years before these articles were published. *Lee* at 4. The HPV-77 DE-5 underlying the *Horstmann* article "became the first rubella vaccine licensed for use in the United States" in 1969. *Id*. However, "[s]oon afterward, other live attenuated RV vaccines became available, and one of these, the RA 27/3 strain, became the mainstay of vaccination programs in most developed countries." *Id*. The medical technology upon which the Petitioners' cited research relied was in its nacency; its efficacy and safety had 25 years to improve before the MMR vaccine was administered to Shon Sumner/S.E.B. in 1996. Pet. Ex. 1 at 1. *Lee*, published in 2000, concluded "[s]ince vaccination does not result in congenital abnormalities when inadvertently given in early pregnancy, comparisons of vaccine strains with wild-type strains may reveal

[43] Pet. Ex. 34, the *Gualberto* article.

important motifs associated with teratogenicity." Pet. Ex. 22 at 15. This conclusion is contrary to the conclusion concerning the teratogenicity of the vaccine reached by *Horstmann* quoted above. *See* Pet. Ex. 33.

The other literature upon which Dr. Bellanti relied was similarly dated: for example, *Orquin* was published in 1981. As Dr. Raymond noted at hearing, this article "is over 30 years old, and the field of study of Aicardi syndrome has moved way beyond that." Tr. at 130; *see also* Pet. Ex. 35. Dr. Bellanti's reliance on this extremely outdated literature is another strike against the reliability of his scientific methodology.

iii. Failure of expert to review his own previous report; failure to read literature cited by opposing expert; misleading citations of medical records and literature.

Petitioners filed Dr. Bellanti's First Expert Report on October 9, 2012. *See* Pet. Ex. 12. In that report, Dr. Bellanti recognized the correct Aicardi syndrome, and that S.E.B. had been diagnosed with Aicardi. *See generally* Pet. Ex. 12. At page 7 of his First Expert Report, after the first reference to Aicardi syndrome set forth in his summary of S.E.B.'s medical records, Dr. Bellanti dropped this footnote: "Aicardi syndrome is a rare genetic malformation syndrome characterized by the partial or complete absence of a key structure in the brain called the corpus callosum, the presence of retinal abnormalities, and seizures in the form of infantile spasms." Pet. Ex. 12 at 7, n.5. His medical records summary then continues with a detailed discussion of the medical conditions from which S.E.B. suffers which supported her many treating physicians' diagnoses of Aicardi. *See generally* Pet. Ex. 12.

Dr. Bellanti's First Report concludes: "Clinical notes on 7/3/97 indicate that [S.E.B.] was an 8-month-old youngster with a diagnosis of Aicardi's [sic] syndrome, developmental delays and seizures. . . .These genetic malformations are direct results of the vaccination that Shon [Sumner] had on March 25, 1996." Pet. Ex. 12 at 26.

By the time of his First Supplemental Report, Dr. Bellanti had purportedly "undertaken a detailed review of the medical literature on Aicardi syndrome." Pet. Ex. 16 at 1. In reality, however, he had merely attached a number of articles about AGS, a condition linked to Aicardi syndrome only by the fact that they were both first discovered and written about by the same doctor, Dr. Jean Aicardi. Pet. Ex. 18-21, 23. In his First Supplemental Report, Dr. Bellanti erroneously described Aicardi as being "characterized by acquired microcephaly, cerebral calcifications, leukodystrophy, poor feeding, jitteriness, cerebral atrophy, problems with white matter, and chilblains-like (scaly or necrotic) skin lesions, usually on the fingers, toes and ears." Pet. Ex. 16 at 1. Clearly this is not the same condition described in his First Report, the condition from which S.E.B. clearly suffers, and which Dr. Bellanti agreed she had. And yet, Dr. Bellanti's First Supplemental Report concludes: "In conclusion, as described in my previous opinion, I believe that it is highly unlikely that [S.E.B.] has Aicardi syndrome, and [S.E.B.]'s current medical conditions of developmental delay, seizures, and ophthalmological damage are to a reasonable degree of medical and scientific certainty more likely than not

caused or contributed to by the MMR vaccine administered to her mother *in utero* [sic] at 28 days gestation." Pet. Ex. 16 at 2.

Another example of Dr. Bellanti's failure to reread his own report and the medical records can be found in his treatment of page 45 of Petitioners' Exhibit 8. In support of his first Report, Dr. Bellanti engaged in a thorough review of S.E.B.'s medical records, and 25 of the report's 26 pages concern an extensive summary of those records. Included in that summary is this lengthy excerpt from Exhibit 8 at 45:

> On **7/3/97,** a letter to pediatric neurolology by Dr. Stephen E. Brooks, Asst. Prof. of ophthalmology and pediatrics states: "I had the opportunity of seeing [S.E.B.] for the first time here in the pediatric eye clinic on 7/1/97 for evaluation of visual function. She is now an eight-month old youngster with a diagnosis of Aicardi's [sic] syndrome. She has developmental delay and seizures for which she is being treated with phenobarbital. Previous eye exam by an outside ophthalmologist apparently revealed a finding of optic nerve hypoplasia. On my examination, [S.E.B.] showed good visual fixation bilaterally with no apparent asymmetry or amblyopia. She had full ocular motility with no apparent strabismus. External exam was significant only possibly for slightly enlarged head circumference. Pupils equal, round, reactive, with no apparent pupillary defect. The anterior segment of each eye was normal but the fundoscopic exam did show characteristic fundus lesions of Aicardi syndrome. Specifically, there were numerous "punched out" lacunar-type lesions throughout both fundiae [sic]. The optic nerve itself may have been slightly dysplastic in the right eye but was essentially of normal size and color. The macula in the right eye was also well-developed. The left eye appeared more severely affected with more numerous and larger lesions including a hyperpigmentation directly overlying a significant portion of the optic nerve. My colleague, Dr. Dennis Marcus, who specializes in Retina, also had a look at the left fundus but felt that the pigmentation overlying the nerve was of benign nature and consistent with a [sic] Aicardi syndrome. The cycloplegic refraction demonstrated a moderate hyperopia bilaterally within normal limits for [S.E.B.]'s age. My impression is that [S.E.B.]'s exam is consistent with Aicardi syndrome. Visual function at this point is clinically within normal limits, but there is certainly an uncertain prognosis especially in the left eye considering the numerous fundus lesions and potential abnormality of the optic nerve which could not be well evaluated owing to the pigmentation. I would like to see [S.E.B.] again at 4 months to recheck visual function and I have set that appointment up already.

First Report at 8-9 (emphasis added). The entire purpose of this letter was for Dr. Brooks to confirm that he and his colleague, Dr. Marcus, both ophthalmologists and faculty members at Medical College at Georgia, had examined S.E.B., and that the lacunar lesions and hyperpigmentation in her eyes were indeed consistent with a diagnosis of Aicardi syndrome, and Dr. Bellanti recognized that purpose in his First Report. Pet. Ex. 12. But in his First Supplemental Report, Dr. Bellanti discusses only the highlighted sentence concerning "slightly

enlarged head circumference" as support for his conclusion that S.E.B. does not have Aicardi syndrome. Pet. Ex. 16 at 2.

Dr. Bellanti opens his First Supplemental Report by saying "[t]his letter is to update my expert opinion in the [S.E.B.] case. . .The following are my rebuttal arguments to those made by Dr. Raymond that [S.E.B.]'s medical conditions are the result of Aicardi syndrome." But at a minimum, the contradictory conclusions noted above demonstrate that Dr. Bellanti did not even review his own first report before preparing his second. Pet. Ex. 16. Nor did Dr. Bellanti read any of the literature cited by Dr. Raymond in support of Respondent's first report. Had Dr. Bellanti made even a cursory review of his own first report and *Sutton*, attached to Dr. Raymond's report, he would have recognized the distinction between AS and AGS, before leading the parties on a wild goose chase after the wrong syndrome. It is a basic tenet of scientific research that one reviews one's own work before supplementing it, and Dr. Bellanti's failure to do so further calls into question the reliability of his scientific methodology, the substance of which is the subject of the remainder of this decision.

2. Petitioners have failed to prove, by a preponderance of the evidence, that a rubella vaccine administered during pregnancy can cause injuries consistent with Aicardi syndrome.

For the reasons that follow, the undersigned finds that Petitioners have failed to articulate a persuasive, reliable theory by which a partial congenital rubella infection could result in an injury that produces signs and symptoms consistent with Aicardi syndrome.

It is unclear to the undersigned whether Dr. Bellanti's theory is that the infection caused the alleged injury by causing a genetic mutation or whether, alternatively, the infection caused the injury by inflicting teratologic damage on the developing fetus. *See* tr. at 45. One interpretation of Petitioners' argument is that environmental factors – i.e., a partial congenital rubella infection from a reverted rubella vaccine that crossed the placenta – caused one of S.E.B.'s X chromosomes to mutate. *See* tr. at 65 (Dr. Bellanti testifying that "[w]e don't know the genetic basis of Aicardi, but we know that there are probably many causes of that or could be, and one of the causes is congenital rubella syndrome").

Another interpretation of Petitioners' argument is that the rubella virus, having reverted and crossed the placenta, caused teratological damage to the developing fetus, causing injuries that later manifested as Aicardi. *See* tr. at 73-74 (Dr. Bellanti noting that, "[o]nce you have congenital rubella syndrome as the cause, then, by definition, it's no longer Aicardi because it's no longer a genetic condition").

Petitioners provided no scientific basis for the first interpretation of their theory, and in light of their statements in support of the second interpretation, it is not clear to the undersigned that this was actually a theory they were advancing. However, in an abundance of caution, the undersigned has analyzed that theory in light of the record before her.

In response to that interpretation, Dr. Raymond agreed that the gene that causes Aicardi syndrome has not yet been identified. Resp. Ex. A-1 at 3. Dr. Raymond argued, however, and Petitioners do not dispute, that there is no known case of a gene mutation resulting from a teratologic agent. *See* Resp. Ex. F at 1-2. He also asserted that "as a teratogenic effect, rubella should be rubella should be rubella. . . . It should result in features consistent with congenital rubella syndrome" rather than by causing the damage characteristic of a genetic mutation, or by causing the mutation itself. Tr. at 149. In addition, Respondent's primary Aicardi reference, the *Sutton* article, states that "[a]t least six pairs of twins who are discordant for Aicardi syndrome are known, five of whom are confirmed dizygotic, excluding the possibility that the etiology is a prenatal toxin or other disruptive event." Resp. Ex. A-1 at 3. As acknowledged by both experts, although the affected gene itself has not been identified, the majority of cases of Aicardi syndrome occur in the absence of a rubella infection. Tr. at 65-67, 96.

Ultimately, in the absence of any evidence that an infection can cause genetic damage, and in light Dr. Raymond's qualifications in teratology and genetics, *see generally* Resp. Ex B; tr. at 108-10, the undersigned declines to find that Petitioners have provided a "sound and reliable scientific explanation" for the theory that a partial congenital rubella infection from a reverted rubella vaccine that crossed the placenta caused one of S.E.B.'s X chromosomes to mutate. *See Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994).

The second interpretation of Petitioners' theory, that the partial rubella infection resulting from the reverted attenuated vaccine virus can cause teratological damage to a fetus that mimics the damage characteristic of Aicardi, was the argument they more rigorously advanced at hearing. Dr. Bellanti argued that "[r]ubella in fetal tissues has a propensity to persist throughout pregnancy;" its clinical expression depends on "the amount of viral replication, the stage at which [the] virus is entered, and … the degree of virulence of the infecting virus," and the partial rubella infection may have affected "any of the organs or tissues of the fetus." Tr. at 33, 88.

The undersigned finds, based on the reliable scientific evidence presented, that the signs and symptoms associated with Aicardi essentially do not overlap with the signs and symptoms associated with CRS. *See* tr. at 96, 120-21 (noting that the eye features and agenesis of the corpus callosum, which are hallmarks of Aicardi syndrome, are rarely, if ever, noted in CRS; the signs and symptoms associated with each syndrome are very dissimilar); s*ee also Willis* at 4 ("The 'salt and pepper' pigmented fundus often seen with congenital syphilis or rubella is distinctly unlike the fundus in the Aicardi syndrome;" "[a]genesis of the corpus callosum, another feature of the Aicardi syndrome, is not found in the infections, except in one doubtful case of congenital rubella.") Moreover, Petitioners have not explained why it is reasonable to believe that a "partial" congenital rubella infection, or a congenital rubella infection acquired from a reverted vaccine that crossed the placenta, or a congenital rubella infection acquired via the bloodstream rather than via the respiratory tract, can cause signs and symptoms that are strikingly dissimilar from those associated with a "full-blown" congenital rubella infection.

The undersigned finds particularly compelling Dr. Raymond's argument that the signs and symptoms associated with Aicardi are qualitatively different from the types of damage

caused by rubella infections; that they are different in kind. Tr. at 114-18. Aicardi, which results from X chromosome inactivation, is a patchy abnormality; CRS, which results from an *in utero* infection that affects cell proliferation, produces a more diffuse abnormality. Tr. at 113-14, 126-27. The undersigned finds that, whether a rubella infection is "full-blown" or "partial," the resulting abnormalities are likely to be diffuse (consistent with abnormal cell proliferation) rather than patchy (consistent with X chromosome inactivation). *See, e.g.*, tr. at 93-96, 120 (Dr. Raymond's discussions of the pigmented fundus that is characteristic of congenital rubella and the lacunar deformation of the eye that is associated with Aicardi).

The undersigned is also perplexed as to how a syndrome that bears not a single symptom characteristic of a congenital rubella infection nor has any serological marker that could confirm congenital rubella infection could nevertheless allegedly be caused by a congenital rubella infection. All of the literature submitted by both experts concerning congenital rubella anticipates being able to confirm the congenital rubella infection diagnosis through symptoms, *see, e.g.*, *Willis* at 4 ("certain associated abnormalities would make a diagnosis of congenital infection more likely than the Aicardi syndrome"), serology, *see* Pet. Ex. 17 at 2-3, or both. *Lee* at 572; Resp. Ex. E at 1-2. None of the submitted literature supports Petitioners' argument that no symptoms *plus* no serology can still equal congenital rubella infection, even a "partial" one.

Although facially supportive of Petitioners' theory, the *Gualberto* and *Orquin* case studies do not constitute reliable evidence that a congenital rubella infection can cause injuries consistent with Aicardi syndrome. As noted by Dr. Raymond, the child referenced in *Orquin* did not meet the WHO criteria for CRS, and her CRS diagnosis was never serologically confirmed. *See* Resp. Ex. F at 1. *Gualberto* – which is the only article cited by Petitioners that concerns the reversion theory – discusses a patient with fulminant encephalitis. Resp. Ex. F at 1. Encephalitis is a known complication of rubella infection; if the vaccine virus did revert to wild-type virus in this single patient, the reverted virus caused damage consistent with what the wild-type virus would cause. *Id.*; tr. at 155-56. *Gualberto* does not support Petitioners' argument that a reverted virus can cause injuries completely uncharacteristic of the injuries associated with the wild-type virus.

For the reasons stated above, the undersigned finds that Petitioners have failed to provide preponderant evidence in support of a reliable theory of causation pursuant to *Althen* Prong One.

b. *Althen* Prong 2.

Assuming, *arguendo*, that a partial congenital rubella infection can cause the injury that manifested in S.E.B. as Aicardi, Petitioners' claim also fails on *Althen*'s second prong. Petitioners' theory hinges upon a series of extremely unlikely events, all of which are required to have happened in succession in order for the vaccine to have caused S.E.B.'s injuries. Tr. at 34-35, 40-48. After vaccination, the attenuated virus would have had to revert to virulence in the absence of any documented symptoms in Ms. Sumner. Tr. at 34-37; 40-45. The virus would then have had to cross the placenta. Tr. at 45. Having crossed the placenta, the virulent

virus would have had to cause a partial infection in the fetus, and the viral load would have had to spike throughout gestation, mutating S.E.B.'s X chromosome and/or otherwise causing her injuries. *See* tr. at 137-38.

The undersigned notes that there has been no serologic confirmation that S.E.B. ever had a rubella infection. Tr. 98-100. As has been generally acknowledged, two serological measurements – IgG and IgM – are the classic criteria for diagnosis of CRS. *See* Resp Ex. E at 2. In both his 1965 article *Congenital Rubella*[44] and during his hearing testimony, Dr. Bellanti asserted that the presence of IgM antibodies in the sera of an affected infant is critical to the diagnosis of CRS. Pet. Ex. 17 at 468, 472; Tr. at 53 ("a very prominent IgM . . . is the hallmark of intrauterine infection. . . .This very high IgM is really a primitive marker . . . and it's useful diagnostically"). One of the essential findings in *Congenital Rubella* was that "[t]he only immunoglobulin which is normally transmitted transplacentally to the newborn is the 7S γG-immunoglobulin. In contrast, each of the six infants in this series showed prominent γM-immunoglobulins [IgM] in their sera." Pet. Ex.17 at 466. Dr. Bellanti testified that the presence of IgM antibody in the baby studied in *Orquin* was "presumptive evidence that there was congenital rubella infection," and that "it was an IgM antibody by the method that they used in that paper, coaxing the diagnosis that it was congenital rubella." Tr. at 33, 84.

The undersigned also finds that none of the classic clinical symptoms of CRS are evident in S.E.B. The classic clinical symptoms supporting a diagnosis of CRS are "congenital heart disease, cataracts, heptosplenomegaly, and thrombocytopenic purpura;" deafness is the most common. Pet. Ex. 17 at 1. *See also* Ex. E; tr. at 61, 118-19. S.E.B. has none of these symptoms. Tr. at 60-61. Nor did S.E.B. exhibit even any of the minor diagnostic characteristics of CRS, save mental retardation, which is a symptom attributable to so many disorders that it cannot be considered to be diagnostic in the absence of other diagnostic criteria. Tr. at 151-52; *see generally* Pet. Ex. E.

The undersigned understands that Petitioners' theory posits that S.E.B. suffered only from a partial rubella infection, and that such infections can exist without any outward manifestations or confirmatory serological results. Tr. at 86-87. But neither Petitioners nor Dr. Bellanti have submitted any medical literature, or any other documentation, regarding the existence of a phenomenon that he refers to as "a partial infection." 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 v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 743 (Fed. Cl. 2009) (emphasis in original) (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 137 (1997)). *See also Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1324 (Fed. Cir. 2010) ("[T]he special master is entitled to require some indicia of reliability to support the assertion of the expert witness.")

Accordingly, the undersigned finds that Petitioners have failed to provide preponderant evidence of a logical sequence of cause and effect under *Althen* Prong Two.

[44] *See supra* note 21.

c. *Althen* Prong 3.

The facts of this case complicate the process of assessing whether Petitioners have made an adequate showing of a proximate temporal relationship between vaccination and injury. *Althen*, 418 F.3d at 1279. It is not disputed that Ms. Sumner received the vaccination when she was between four and eight weeks pregnant, and that S.E.B. was born with her injuries. *See* Resp. Ex. A at 1; Pet. Ex. 12 at 3. It is also not disputed that the formation of the corpus callosum occurs at 14 to 18 weeks gestation. Tr. at 124.

The undersigned finds that agenesis of the corpus callosum and heterotopias, both of which are major characteristics of Aicardi syndrome and both of which are evident in S.E.B., are critical to the temporal component of *Althen*. *See Sutton* at 1-2; tr. at 116-17. The timeframe in which these brain structures manifest in a developing fetus has been definitively established: "[t]he development of the corpus callosum occurs between 14-18 weeks gestation and disorders of neuronal migration that result in formation of the heterotopias occur at 20-23 weeks gestation." Resp. Ex. A at 4; tr. 124. Thus, formation of the relevant structures of S.E.B.'s brain did not occur until at least six weeks after administration of the vaccine.

The undersigned acknowledges Petitioners' arguments that "[r]ubella in fetal tissues has a propensity to persist throughout pregnancy," and that the viral load can "spike" at different times after vaccine administration. Tr. 88, 137-38. The undersigned notes, however, that according to Petitioners' own medical literature, even an acknowledged rubella infection is unlikely to cause defects after the first trimester: while "the fetus can still be infected [with rubella] after the first trimester," there are unlikely to be any congenital defects after 18-20 weeks gestation. *Lee* at 584. Moreover, as Dr. Raymond argued, in S.E.B.'s case a rubella infection in the fetus would have affected fetal development throughout the first trimester, causing "much wider and different abnormalities to the brain" than those S.E.B. sustained. Tr. at 126.

The undersigned concludes that Petitioners have failed to prove, by a preponderance of the evidence, that there is a proximate temporal relationship between the administration of the MMR vaccine and the injuries that manifested as Aicardi syndrome in S.E.B.

IV. Conclusion

The undersigned has no doubt that S.E.B. is now a profoundly challenged young woman with significant ongoing needs. However, those compelling circumstances standing alone cannot be the basis of a vaccine award. The undersigned finds that Petitioners have failed to put forward a reliable theory of vaccine causation and have not established with reliable evidence that S.E.B. has congenital rubella syndrome or Aicardi syndrome caused by the rubella component of the MMR vaccine.

The only reliable evidence offered in the case proves that Petitioner Shon Sumner received an MMR vaccine; that the vaccine was passed through to the *in utero* S.E.B. in the

form of immunity (elevated IgG for rubella); and that S.E.B. was born with a genetic malformation whose symptoms are known as Aicardi syndrome. There is no other reliable evidence tying the one to the other. The Petition must therefore be, and is, **DISMISSED**.

In the absence of a motion for review filed pursuant to RCFC Appendix B, the clerk of the court **SHALL ENTER JUDGMENT** accordingly.

IT IS SO ORDERED.

s/Lisa Hamilton-Fieldman
Lisa Hamilton-Fieldman
Special Master