In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 15-1186V
Filed: January 18, 2022
PUBLISHED

MANDY BANGERTER, parent and next friend of D.B., a minor,

Petitioner,

v.

SECRETARY OF HEALTH AND HUMAN SERVICES,

Respondent.

Special Master Horner

Infantile Spasms; Tetanus, diphtheria, acellular pertussis ("DTaP") vaccine; Pneumococcal Conjugate Vaccine; Residual Effects and Complications

Richard Gage, Richard Gage, P.C., Cheyenne, WY, for petitioner.
Julia Marter Collison, U.S. Department of Justice, Washington, DC, for respondent.

DECISION[1]

On October 13, 2015, petitioner filed a petition under the National Childhood Vaccine Injury Act, 42 U.S.C. § 300aa-10-34 (2012),[2] alleging that her child, D.B., suffered infantile spasms following his receipt of various childhood vaccinations[3] on February 14, 2014. (ECF No. 1.) For the reasons set forth below, I conclude that petitioner is not entitled to compensation.

[1] Because this decision contains a reasoned explanation for the special master's action in this case, it will be posted on the United States Court of Federal Claims' website in accordance with the E-Government Act of 2002. *See* 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services). **This means the decision will be available to anyone with access to the Internet.** In accordance with Vaccine Rule 18(b), petitioner has 14 days to identify and move to redact medical or other information the disclosure of which would constitute an unwarranted invasion of privacy. If the special master, upon review, agrees that the identified material fits within this definition, it will be redacted from public access.

[2] Within this decision, all citations to § 300aa will be the relevant sections of the Vaccine Act at 42 U.S.C. § 300aa-10-34.

[3] Specifically, diphtheria, tetanus and acellular pertussis ("DTaP"), Hepatitis B, Inactivated Polio Vaccine ("IPV"), Haemophilus Influenzae type B ("HIB"), Pneumococcal Conjugate 13-Valent, and Rotavirus. (ECF No. 1.)

AUTHENTICATED U.S. GOVERNMENT INFORMATION GPO

I. Applicable Statutory Scheme

Under the National Vaccine Injury Compensation Program, compensation awards are made to individuals who have suffered injuries after receiving vaccines. In general, to gain an award, a petitioner must make a number of factual demonstrations, including showing that an individual received a vaccination covered by the statute; received it in the United States; suffered a serious, long-standing injury; and has received no previous award or settlement on account of the injury. Finally – and the key question in most cases under the Program – the petitioner must also establish a *causal link* between the vaccination and the injury. In some cases, the petitioner may simply demonstrate the occurrence of what has been called a "Table Injury." That is, it may be shown that the vaccine recipient suffered an injury of the type enumerated in the "Vaccine Injury Table," corresponding to the vaccination in question, within an applicable time period following the vaccination also specified in the Table. If so, the Table Injury is presumed to have been caused by the vaccination, and the petitioner is automatically entitled to compensation, unless it is affirmatively shown that the injury was caused by some factor other than the vaccination. § 300aa-13(a)(1)(A); § 300 aa-11(c)(1)(C)(i); § 300aa-14(a); § 300aa-13(a)(1)(B).

In many cases, however, the vaccine recipient may have suffered an injury *not* of the type covered in the Vaccine Injury Table. In such instances, an alternative means exists to demonstrate entitlement to a Program award. That is, the petitioner may gain an award by showing that the recipient's injury was "caused-in-fact" by the vaccination in question. § 300aa-13(a)(1)(B); § 300aa-11(c)(1)(C)(ii). In such a situation, of course, the presumptions available under the Vaccine Injury Table are inoperative. The burden is on the petitioner to introduce evidence demonstrating that the vaccination actually caused the injury in question. *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005); *Hines v. Sec' of Health & Human Servs.*, 940 F.2d 1518, 1525 (Fed. Cir. 1991).

The showing of "causation-in-fact" must satisfy the "preponderance of the evidence" standard, the same standard ordinarily used in tort litigation. § 300aa-13(a)(1)(A); *see also Althen*, 418 F.3d at 1279; *Hines*, 940 F.2d at 1525. Under that standard, the petitioner must show that it is "more probable than not" that the vaccination was the cause of the injury. *Althen*, 418 F.3d at 1279. The petitioner need not show that the vaccination was the sole cause of the injury or condition, but must demonstrate that the vaccination was at least a "substantial factor" in causing the condition, and was a "but for" cause. *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999). Thus, the petitioner must supply "proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury;" the logical sequence must be supported by "reputable medical or scientific explanation, *i.e.*, evidence in the form of scientific studies or expert medical testimony." *Althen*, 418 F.3d at 1278; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). A petitioner may not receive a Vaccine Program award based solely on his or her assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. § 300aa-13(a)(1).

In what has become the predominant framing of this burden of proof, the *Althen* court described the "causation-in-fact" standard, as follows:

> Concisely stated, Althen's burden is to show by preponderant evidence that the vaccination brought about her injury by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of proximate temporal relationship between vaccination and injury. If Althen satisfies this burden, she is entitled to recover unless the [government] shows, also by a preponderance of the evidence, that the injury was in fact caused by factors unrelated to the vaccine.

Althen, 418 F.3d at 1278 (citations omitted). The *Althen* court noted that a petitioner need not necessarily supply evidence from medical literature supporting petitioner's causation contention, so long as the petitioner supplies the medical opinion of an expert. *Id*. at 1279-80. The court also indicated that, in finding causation, a Program fact-finder may rely upon "circumstantial evidence," which the court found to be consistent with the "system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." *Id*. at 1280.

II. Procedural History

This case was initially assigned to Special Master Millman. (ECF No. 4.) Thereafter, petitioner filed medical records, Exhibits 1-3, to support her claim. (ECF No. 8.) On January 19, 2016, an initial status conference was held during which Special Master Millman ordered petitioner to file additional supportive documentation, including affidavits from D.B.'s treating physicians. (ECF No. 9.) Special Master Millman noted that she "does accept that the DTaP vaccination could have caused D.B.'s infantile spasms," however, her review of the records revealed that D.B.'s developmental delay may have predated his receipt of the vaccinations at issue. (*Id*. at 1-2.) Additionally, she noted that "even if petitioner can prove that the vaccines significantly aggravated D.B.'s developmental delays, petitioner's medical records do not show that D.B. experienced more than six months of sequalae."[4] (*Id*. at 2.)

Thereafter, petitioner filed additional records, Exhibits 4-8, and a letter from Dr. Robert Leland, D.B.'s pediatrician, Exhibit 9. (ECF Nos. 10, 12, 14.) Petitioner also filed additional medical records (Exs. 10, 11). (ECF Nos. 20, 31.) On June 23, 2017, petitioner filed a preliminary opinion letter from Dr. Harum, a pediatric

[4] Of note, it is undisputed that D.B. had Down syndrome prior to onset of his infantile spasms; however, petitioner does not contend that this case constitutes a significant aggravation claim with respect to D.B.'s preexisting developmental delay. (ECF No. 1; ECF No. 108, p. 1.) Rather, petitioner contends that D.B.'s infantile spasms represent a separate condition from his developmental delay, but one which did also affect his developmental progress. (*Id*.) The parties do disagree as to whether that condition was caused-in-fact by his vaccinations and whether residual effects of that condition interfered with his development for more than six months. However, petitioner's arguments regarding the residual effects of D.B.'s infantile spasms also go beyond allegations of developmental delay.

neurodevelopment specialist, indicating that D.B.'s development had been affected for more than six months following his infantile spasms. (ECF No. 40; Exs. 12-13.) Petitioner filed a full report by Dr. Harum (Ex. 15) and further records (Ex. 14) on August 9, 2017. (ECF No. 42.) Special Master Millman ordered petitioner to file a clarifying report by Dr. Harum, which was filed on November 6, 2017, with accompanying literature. (ECF Nos. 43-44; Ex. 16-19.) Additionally, on January 16, 2018, petitioner filed an opinion from neurologist Dr. Marcel Kinsbourne, with accompanying curriculum vitae and medical literature. (ECF No. 46; Exs. 20-23.)

Respondent filed his Rule 4(c) report on April 30, 2018, recommending against compensation. (ECF No. 51.) Thereafter, petitioner filed a supplemental expert report by Dr. Kinsbourne and additional medical literature on August 15, 2018. (ECF No. 54; Ex. 24-38.) Additional medical records were filed in December of 2018. (ECF No. 60; Ex. 39.) Respondent filed a responsive expert report and supporting literature from neurologist Dr. Gregory L. Holmes on February 4, 2019. (ECF No. 61; Ex. A.) Petitioner filed a further supplemental report and literature Dr. Kinsbourne on May 17, 2019. (ECF No. 67; Ex. 40-48.)

This case was then reassigned to my docket on June 6, 2019, due to Special Master Millman's retirement. (ECF No. 69.) Thereafter, the parties filed further supplemental expert reports. (ECF No. 70; Ex. C and ECF No. 71; Exs. 49-51 and ECF No. 72; Ex. D.) However, on December 30, 2019, petitioner filed a status report indicating that, after filing five expert reports, petitioner did not "feel that filing additional expert reports will be beneficial," and requested a hearing. (ECF No. 74.) Respondent agreed and a hearing was scheduled. (ECF Nos. 76-77.) Thereafter, the parties filed substantial additional medical literature in the lead up to the entitlement hearing.[5] (ECF Nos. 83, 89, 91, 94-97, 100; Exs. 52-92.)

[5] As noted above, Special Master Millman, the previously assigned special master, had indicated during a prior status conference her acceptance that the DTaP vaccine can cause infantile spasms. (ECF No. 9.) Thus, for example, in a November 19, 2020 prehearing brief, petitioner cited, *inter alia*, a ruling by Special Master Millman, in *Kottenstette v. Sec'y of Health & Human Servs.*, in which she found that the petitioners had demonstrated that infantile spasms can be caused by the DTaP vaccine. ECF No. 88, p. 9 (citing No. 15-1016V, 2017 WL 6601878 (Fed. Cl. Spec. Mstr. Dec. 12, 2017).) However, on February 12, 2020, and subsequent to Special Master Millman's retirement, that ruling was vacated by the Court of Federal Claims on the basis that she had applied an incorrect legal standard. *Kottenstette*, No. 15-1016V, 2020 WL 953484 (Fed. Cl. Feb. 12, 2020).

Due to the retirement of the previously assigned special master, the case had been reassigned to me and, thus, was remanded to me for evaluation of petitioner's theory consistent with the correct legal standard. *See id.* On June 2, 2020, I issued a decision on remand reaching a different result from Special Master Millman. *See Kottenstette*, No. 15-1016V, 2020 WL 4197301 (Fed. Cl. Spec. Mstr. June 2, 2020). In that decision I concluded that, although petitioners had demonstrated that the Tdap vaccine can cause febrile seizures, there was not preponderant evidence that it can cause the specific disorder of infantile spasms. *Id*. at *13-14. The outcome of my analysis then turned on factors related to *Althen* prong two. *Id.* at *15-17. Because there was not preponderant evidence that the *Kottenstette* child suffered a febrile seizure, I did not reach the question under *Althen* prong one of whether a single febrile seizure could ultimately lead to the type of epileptic encephalopathy implicated by the condition of infantile spasms. *Id*. at n. 37.

A two-day entitlement hearing was held on December 17 and 18, 2020. (*See* ECF No.104-05, Transcript of Proceedings ("Tr"), filed 1/21/2021). Petitioner, D.B.'s mother, and Jedidiah Bangerter, D.B.'s father, both testified. Petitioner also presented testimony by Drs. Harum and Kinsbourne as well as by D.B.'s occupational therapist, Sarah Nicholas. Respondent presented expert testimony from Dr. Holmes. Petitioner filed a post-hearing brief on March 18, 2021, and respondent filed his response on May 12, 2021. (ECF Nos. 108-09.) Petitioner did not file any reply.

After the parties filed their post-hearing briefs, the Federal Circuit issued its decision *Wright v. Secretary of Health and Human Services*, which interpreted the statutory language pertaining to the Vaccine Act's severity requirement (42 USC § 300aa-11(c)(1)(D)). No. 2021-1524, 2022 WL 38987 (Fed. Cir. Jan. 5, 2022). The parties were given an opportunity to file supplemental briefs addressing this new authority. The parties filed those briefs on January 14, 2022. (ECF Nos. 113-14.)

This case is now ripe for consideration. In total, petitioner has filed 92 numbered exhibits, including medical records (Exs. 1-7, 10-11, 14, 39), expert and treater opinion evidence (Ex. 8-9, 12-13, 15, 20, 23-24, 40, 49), and medical literature (Exs. 17-19, 25-38, 41-48, 50-92).[6] Respondent filed responsive expert reports (Exs. A-D) and supporting literature (Ex. A, Tabs 1-37, and Exs. E-L).[7] Although this decision does not

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In response, petitioner in this case sought to supplement the record during the prehearing phase of proceedings to address points raised in my own analysis of the *Kottenstette* case as compared to that of Special Master Millman. These filings were permitted, even though many constituted late-filed evidence pursuant to the prehearing order. At the close of the hearing, I noted: "the last point to address would be during the prehearing status conference, we talked about the extent to which Mr. Gage wanted to add to the record in light of *Kottenstette*, my decision is *Kottenstette*. It looks to me as though we've done that, and I think Ms. Collison and Dr. Holmes have responded to the articles that Mr. Gage filed. So I just want to confirm with everybody, do we have a complete record at this point?" (Tr. 356.) Both counsel confirmed the record to be complete. (Tr. 356-57.) Ultimately, neither party further addressed *Kottenstette* in their post-hearing briefs. (ECF Nos. 108-09.)

Subsequent to my decision on remand in *Kottenstette*, the Court of Federal Claims denied a further motion for review and the Federal Circuit ultimately issued a decision in *Kottenstette* reversing the Court of Federal Claims and reinstating Special Master Millman's initial ruling in favor of entitlement. No. 15-1016V, 2020 WL 4592590 (Fed. Cl. Jul. 27, 2020), *rev'd* 861 Fed.Appx. 433 (2021). However, the Circuit's analysis of the remand decision focused on the fact that it exceeded the scope of the remand by including a reweighing of the evidence.

[6] However, quite a few exhibits were duplicated largely for purposes of adding highlighting to key passages. Exhibits 41, 57-82, and 90, duplicate previously filed exhibits.

[7] Some of respondent's exhibits likewise overlap with exhibits previously filed by petitioner. For example, in response to Dr. Kinsbourne's reliance on studies by Bellman, Melchior, discussed extensively below, Dr. Holmes refiled the same exhibits highlighting the passages he felt most significant and also filed a related study, also discussed below, by Goodman. Dr. Kinsbourne later refiled the Goodman study in his further report. Thus, the Bellman study has been filed as Exhibit A, Tab 16, in addition to being marked as petitioner's Exhibits 28, 65, and 90. The Melchior study has been filed as Exhibit A, Tab 17, as well as being filed as petitioner's Exhibits 34 and 71. The Goodman study has been filed as Exhibit A, Tab 18, as well as being filed as petitioner's Exhibit 42.

explicitly cite every article filed by the parties, each has been reviewed and the analysis herein is based on the record as a whole.

III. Factual History

a. As Reflected by the Medical Records

D.B. was born on July 22, 2013 with Down syndrome and chronic lung disease. (Ex. 1, p. 1-5; Ex. 39, pp. 6-8.) He was born preterm at 34 weeks and 6 days and spent 40 days in the NICU following delivery. (Ex. 1, p. 5; Ex. 10, p. 6.) He received the Hepatitis B vaccine on the day of his birth. (Ex. 39, p. 10.) On September 3, 2013, D.B., at six weeks old, had a well child visit with Dr. Joseph Horam at Cheyenne Regional Medical Center. (Ex. 1, p. 4.) D.B. had feeding and reflux issues and needed supplemental oxygen. (*Id*. at 5-6; Ex. 2, pp. 4-5.) D.B. was referred to physical and occupational therapies and speech services. (*Id*. at 9; Ex. 2, p. 5.) Additionally, his history of pulmonary hypertension was found to be resolved by October 18, 2013 by Dr. Michael Schaffer. (Ex. 1, p. 10.) D.B. underwent two genetic screenings, which were noted by Dr. Robert Leland, pediatrician, as normal. (*Id*. at 23.)

At two months old, D.B. was evaluated under the Peabody Developmental Motor Scales. (Ex. 3.) In adjusting for his prematurity, D.B. tested, on a scale of zero to two, a two on reflexes and a one on grasping and visual integration at the age of 29 days. (*Id*. at 2.) He also had his initial occupational therapy exam on September 26, 2013. (*Id*. at 19.) Overall, D.B. had low oral muscle tone which contributed to his difficulties with feeding. Also, D.B. "continue[d] to demonstrate immature neurobehavioral cues when overstimulated, including hiccoughing, arching, color change, stop sign, shutting down, eye gaze aversion." (*Id*. at 20.)

On September 27, 2013, D.B. saw Dr. Robert Leland for his 2-month well child visit. (Ex. 1, p. 9.) At this visit, Dr. Leland noted that D.B.'s development was appropriate. (*Id*. at 11.) He returned a month later for a follow up appointment and complained of significant nocturnal choking. (*Id*. at 13.) D.B.'s GERD (gastroesophageal reflux disease) worsened and he saw Dr. Leland again on November 7, 2013. (*Id*. at 16.) Additionally, Dr. Leland reported that D.B. experienced intermittent stridor. (*Id*.) At the next follow up visit, Dr. Leland ordered nocturnal oximetry and sleep study and referred D.B. to a gastroenterology specialist. (*Id*. at 18-19.) At his 4-month check up on November 27, 2013, D.B. was assessed as healthy and his choking has improved. (*Id*. at 23-24.) On December 20, 2013, D.B. received a Synagis injection, which he tolerated well with no reaction at site. (Ex. 1, p. 25.) However, the next day, D.B.'s dad called the hospital concerned with D.B.'s lethargy and lack of appetite following injection. (*Id*. at 25-26.)

D.B. saw Dr. Leland on January 9, 2014 for concern of D.B.'s GERD and Down syndrome. (Ex. 1, p. 27.) Dr. Leland noted that D.B. was now only on nocturnal oxygen, and although there is a procedure, fundoplication, Dr. Leland opined that D.B.'s reflux needs to be reviewed once again. (*Id*. at 28.)

On February 1, 2014, at the advice of the triage nurse on an after-hours call, D.B. went to the emergency department at Cheyenne Regional Medical Center for a croupy cough. (Ex. 1, pp. 32-33.) Dr. Daniel Possehn's impression was that D.B. maybe had bronchiolitis as evident by the coarse lung markings. (*Id*. at 34, 118; Ex. 4, p. 1.) Upon his discharge from the emergency department, D.B. had a follow up appointment with Dr. Carol Schiel, who assessed him with croup, an infection that causes the throat to swell. (Ex. 1, pp. 37-39.) D.B. had a therapy session on January 30, 2014, where D.B.'s mom reported that D.B. was able to roll over independent and the therapy noted that D.B. "tolerates tummy well. Using good elbow prop up to 20 seconds with neck extension." (Ex. 3, p. 22.)

On February 14, 2014, D.B. returned to Dr. Leland for a six-month well child visit. At this visit, Dr. Leland indicated that "[g]rowth parameters are noted and are appropriate for age." (Ex. 1, p. 43.) At this visit, D.B. received DTaP, HiB, Pneumococcal, IPV, Hep B, and rotavirus vaccinations. (*Id*. at 44.) Three days later on February 17, 2014, petitioner called Dr. Leland's office to report that D.B. appeared to be having seizures. (Ex. 1, p. 46.) Dr. Leland suspected infantile spasms and ordered an EEG and consultation from Dr. Dingman, neurologist. (*Id*. at 47.) At this visit, Dr. Leland did assess D.B. with otitis media. (*Id*. at 48.) He was treated with amoxicillin.

The next day on February 18, 2014, D.B. was seen at the hospital for seizures and was admitted for infantile spasms. (Ex. 2, p. 7; Ex. 7, p. 6.) It was reported that D.B. had onset of abnormal movements on February 14, 2014. (Ex. 2, p. 12.) The attending physician, Dr. Kaitlin M. Widmer, noted that D.B. appeared to have met his milestones as a six-month old. (*Id*.) D.B. had a neurology consult during his stay with Dr. Jennifer Armstrong-Wells. (*Id*. at 16.) Her impression was that D.B. "is a 6 month old boy with trisomy 21 and new abnormal spells. On video, these spells are classic for infantile spasms." (*Id*.) Dr. Andra L. Dingman examined D.B. in a follow up neuro consult and after reviewing his EEG, wanted to proceed with ACTh[8] treatment. (*Id*. at 27.) D.B. was discharged on February 19, 2014 with a diagnosis of infantile spams, with secondary diagnoses of Trisomy 21 and acute otitis media. (*Id*. at 8.) At discharge, it was confirmed that D.B. experienced infantile spasms as there was evidence of hypsarrhythmia[9] on his EEG. (*Id*.) D.B. was discharged home to wait for insurance approval of ACTh treatment. (*Id*.)

[8] "ACTh" stands for adrenocorticotropic hormone, an established treatment for infantile spasms. (Nabbout et al., *Infantile Spasms in Down Syndrome: Good Response to a Short Course of Vigabatrin,* 42(12) EPILEPSIA 1580-1583 (2001) (Ex. 21, p. 4); Baram & Hatalski, *Neuropeptide-mediated excitability: a key triggering mechanism for seizure negation in the developing brain,* 21(11) TRENDS. NEUROSCI. 1-9, 6 (1998) (Ex. 26); Tr. 200-01, 293-94.)

[9] "Hypsarrhythmia" is an electroencephalographic abnormality sometimes observed in infants, with random, high-voltage slow waves and spikes that arise from multiple foci and spread to all cortical areas. *Hypsarrhythmia*, DORLAND's ILLUSTRATED MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=24469, last accessed January 11, 2022.

The following day after discharge, D.B. had a therapy session. (Ex. 3, p. 24; Ex. 5, p. 1.) D.B.'s mom reported that he had lost some head control and was not rolling over as much as before and noted that "this may be due to seizure activity." (Ex. 3, p. 24.) During the session, D.B. was able to complete a roll three times.[10] (*Id*.)

On February 26, 2014, D.B. was admitted again to initiate ACTh treatment for his infantile spasms. (Ex. 1, p. 52; Ex. 2, p. 59; Ex. 7, p. 64.) D.B.'s parent noted regression in his milestones, including decreased smiling and babbling, and less neck control, but he did not have any new types of spells. (Ex. 2, pp. 61, 67.) His brain MRI noted mild brachycephaly and nonspecific fluid signal in the left mastoid air cells and middle ear, but was otherwise a "negative MRI." (Ex. 1, p. 57; Ex. 2, pp. 78, 99.) D.B. was discharged on March 1, 2014 with a diagnosis of infantile spasms and secondary diagnoses of leukopenia and Trisomy 21. (Ex. 2, p. 56.) It was noted that "[m]ost spams will stop after the first week of ACTh treatment." (*Id*. at 72.) At discharge, D.B. was ordered to follow up with his PCP during his ACTh treatment. (*Id*. at 57.)

On March 6, 2014, D.B. was examined by Dr. Andrew Rose for a reevaluation of infantile spasms. (Ex. 1, p. 58.) Dr. Rose indicated that D.B. was on ACTh therapy and that D.B. had significant fluid retention. (*Id*. at 59.) D.B. saw Dr. Leland following his stay at the hospital on the same day. (Ex. 1, p. 52.) Dr. Leland indicated that D.B.'s EEG showed hypsarrhythmia and he was diagnosed with infantile spasms. (*Id*.) Dr. Leland prescribed him with ACTh (twice a day for two weeks and then will be tapered down) and ordered electroencephalograms coinciding with his therapy treatment. (*Id*.) Additionally, Dr. Leland indicated that D.B.'s infantile spasms had "diminished remarkably." (*Id*. at 53.)

A couple of days later on March 10, 2014, D.B. visited Dr. Leland and reported that after three days of ACTh, D.B. did not have any further spasms.[11] (Ex. 1, p. 60; Ex. 2, p. 171.) During a reevaluation with Dr. Rose on March 21, 2014, D.B. was noted to be more interactive, but there were still some breathing issues. (Ex. 1, pp. 69-70.) Dr. Rose indicated that the ECHO and EEG were normal and did not show any hypsarrhythmia. (Ex. 1, pp. 69-70; Ex. 11, pp. 1-2.)

D.B. had a therapy session on March 27, 2014, where he was noted to show developmental improvement by sitting independently for 2-3 seconds. (Ex. 3, p. 28; Ex. 5, p. 5.) He also met two of his ongoing short-term feeding goals. (*Id*.) D.B. was responding to therapy, but still demonstrated low oral tone. (Ex. 3, p. 32.) The therapy progress notes indicated that D.B. was being treated for his infantile seizures. (*Id*.) D.B. continued working on his feeding issues with therapy.[12]

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[10] D.B. had a similar therapy session on March 6, 2014 as well. (Ex. 3, pp. 26-27.)

[11] D.B.'s parents also confirmed on the March 13, 2014 visit with Dr. Leland that D.B. has not had any seizures. (Ex. 1, p. 63.) Dr. Andrew White, who interpreted D.B.'s EEG study on March 11, 2014, noted that D.B. did not have any new spasms since March 3, 2014. (Ex. 2, p. 171; Ex. 7, p. 162.)

[12] The April 17, 2014 therapy records no longer indicated infantile seizures as part of D.B.'s assessment. And during this session, D.B. was noted to show improvement through accepting solids from spoon. (Ex.

In a further reevaluation with Dr. Rose, on April 1, 2014, D.B.'s mother (petitioner) reported that D.B. was "back to his normal self. Starting to hold head up, makes noises, and sit up for a few seconds by himself." (Ex. 1, p. 72.) D.B. had his last ACTh dose on April 4, 2020. (*Id*. at 77.) His EEG performed on April 7, 2014, indicated normal results. (Ex. 7, p. 166.) On April 8, 2014, D.B. saw Dr. Andra Dingman for a follow up of his infantile spasms. (Ex. 7, p. 169.) By this visit, D.B. had stopped ACTh treatment for a week and no spasms had occurred since March 3, 2014. (*Id*.) Dr. Dingman noted that in the past week since stopping ACTh treatment, D.B.'s parents reported that he regained his social skills, was smiling often, and showed improvement with head control. (*Id*. at 170.) Dr. Dingman indicated that D.B. responded well to ACTh and the infantile spasms were resolved with normalized EEG. (*Id*. at 173.) However, Dr. Dingman noted that "specific developmental consequences for [D.B.] are hard to predict at this point, but he is at higher risk of more developmental delays than if he has not developed spasms." (*Id*.)

On April 14, 2014, D.B. visited Dr. Leland due to worsening reflux and vomiting. (Ex. 1, p. 80.) Although D.B. had reflux issues, prior to the onset of infantile spasms, he had normal upper GI. (*Id*.) Dr. Leland planned to discuss with D.B.'s pediatric gastroenterologist, Dr. Brumbaugh; however, scheduling did not permit D.B. to be seen until May. (*Id*. at 80-81.) Over the next few days, D.B.'s symptoms continued to worsen, and Dr. Leland assessed that he needed an endoscopy. (*Id*. at 82.) Dr. Leland noted that "[i]t is unclear if his current symptoms [of poor feeding/intake and vomiting] are related to his ongoing reflux." (*Id*.) D.B. did manage to see Dr. David. E. Brumbaugh on April 21, 2014. (Ex. 7, p. 198.) His impression was that D.B.'s reflux now includes an onset of "more forceful emesis and decreased intake," and suggested that the ACTh therapy could increase risk for peptic disease and cortisol deficiency. (*Id*.) Dr. Brumbaugh recommended D.B. stay at the hospital for monitoring due to his high risk of severe dehydration. (*Id*.) D.B. went to the hospital and was admitted for decreased oral intake. (Ex. 1, p. 85.) D.B. had an upper intestinal endoscopy with biopsy on April 22, 2014. (Ex. 7, p. 249.) He was discharged on April 23, 2014. (Ex. 7, p. 229.) Following his stay at Children's hospital, D.B. saw Dr. Danae Stampfli on April 25, 2014. (Ex. 1, p. 85-86.) The plan was to monitor his intake.

D.B. continued to have feeding difficulties and saw Dr. Leland on June 3, 2014. (Ex. 1, p. 87.) Dr. Leland noted that there was less refluxing and only mild choking. D.B. was able to roll from his stomach to his back, sit independently (but tipped over), and other activities. Dr. Leland stated however that "[w]hen he was on ACTh, his weight went past the 95th percentile for a Down syndrome chart. Currently his weight is falling midway between the 75th and 95th percentile." (*Id*.)

Additionally, D.B. continued seeking testing for his bilateral hearing loss. (Ex. 7, p. 345-46.) On July 3, 2014, D.B. was recommended for hearing aid fitting and continued follow-up with audiology. (*Id*.) D.B. had "a bilateral mild sensorineural hearing loss diagnosed shortly after being referred on his newborn hearing screen age."

3, pp. 34-35.) He continued therapy, however, occasionally, he would experience vomiting and serious reflux issues. (*Id*. at 36-44.)

(*Id*. at 346.) It was noted that "[d]evelopmentally, he is delayed although making gains. He had significant regression while he had infantile spasms but has been regaining skills and is almost back to his pre-seizure status." (*Id*.) Dr. Kristina Kocsis indicated that D.B.'s hearing loss was most likely caused by a non-syndromic gene rather than being related to his Down syndrome. (*Id*.)

During his follow up visit on July 8, 2014, with Dr. Dingman regarding the infantile spasms, it was noted that D.B. gained back the milestones that were lost after the onset of spasms and continued making developmental gains. (Ex. 7, p. 351.) From a developmental standpoint, D.B. was reported to be "doing well." (*Id*. at 355.)

At his 12-month checkup, D.B. was still taking Prevacid and progressing slowly regarding his feeding issues. Dr. Leland noted that "Mother is hesitant about immunization as [D.B.'s] infantile spasms began the evening after his 3rd DTAP." (Ex. 1, p. 90.) No additional vaccinations were administered at this appointment; and Dr. Leland answered in the negative when asked if D.B. had a history of previous adverse reactions to immunizations. (*Id*. at 91.) Also, by July 31, 2014, D.B. had met his goal in occupational therapy in demonstrating age-appropriate oral skills in eating puree from a spoon, propping on elbows in prone, and holding head up in play. (Ex. 3, p. 44.) However, during this session, it was first noted as part of his assessment that D.B. had delayed milestones. (*Id*. at 43.) Two months later, his progress notes specified that D.B. demonstrated "low tone throughout and delayed milestones, consistent with Down syndrome." (*Id*. at 50.)

When D.B. was 14 months old, he experienced an upper respiratory infection ("URI") that lasted several weeks. (Ex. 1, pp. 94, 99.) A note left by RN Anna M. Hernandez indicated that RN Hernandez notified that the DT vaccine is available for D.B. and petitioner indicated that D.B. will probably receive it the following day on December 5, 2014. There is no record of D.B. receiving this vaccine, and in fact during a later appointment, Dr. Leland noted that D.B. still needs the DT vaccine. (*Id*. at 102.)

On December 12, 2014, Dr. Leland saw D.B. and noted that he "has two words and eight signs. He sits well. He rolls both ways. He is not crawling, but he scoots on his bottom to get where he wants to go. He is not pulling to stand yet." (Ex. 1, p. 102; Ex. 4, p. 3.) At this visit, D.B. received a diphtheria/tetanus ("DT") immunization, and about three days later, D.B. started experiencing vomiting and diarrhea. (Ex. 4, p. 6.) D.B. returned to see Dr. Leland on December 22, 2014. (*Id*.) Dr. Leland noted the temporal association with the immunizations but also noted that D.B.'s brother also experienced the symptoms two days prior to D.B. (*Id*.) Additionally, Dr. Leland noted that D.B. is less active than usual and ordered stool studies. (*Id*.) About four days later, D.B.'s mom reported that D.B. was feeling better. The stool culture results were negative. (*Id*. at 10.)

In January 2015, D.B. was still undergoing skilled occupational therapy to address his difficulty with oral feeding, low oral tone, and signs of stress with

overstimulation. (Ex. 3, pp. 69-70.) He still had a "sensory and motor dysfunction with swallowing thin liquids." (*Id*. at 69.)

At his 18-month well child visit, Dr. Leland noted that D.B.'s behavior was normal for his age. (Ex. 4, p. 14.) Dr. Leland indicated that D.B. could walk quickly, walk on steps, scribble with crayon, play with building blocks, and feed using a spoon and cup. (*Id*. at 16.) Additionally, regarding his mental development, D.B. had a 15-20 word vocabulary and could form short sentences. (*Id*. at 17.) On February 17, 2015, D.B. was sick with symptoms of URI, coughing, and vomiting. (*Id*. at 21.) His cough persisted over the next couple of days. (*Id*. at 24.) D.B. had other episodes of URI. (*Id*. at 29.) However, during his interval visit on May 8, 2015, Dr. Leland noted that D.B. was making excellent progress despite his history of infantile spasms. (*Id*. at 33.)

At his two-year-old checkup, Dr. Leland indicated that D.B. was a healthy two-year-old with normal growth and development. (*Id*. at 41.) He continued to make progress, although D.B. was becoming ill often and petitioner expressed concern about his immune status in January of 2016. (*Id*. at 64-65.) Dr. Leland indicated he would order bloodwork and a recheck in six months (*Id*. at 65); however, no further pediatric records have been filed. D.B. also continued with his skilled occupational therapy for his Down syndrome and swallowing difficulties. (*See generally* Exs. 5, 14.) Petitioner filed occupational therapy records through June of 2017, at which time D.B. was approximately 47 months of age. (Ex. 14.)

b. As Reflected by Testimony/Affidavits

i. Petitioner Mandy Bangerter's Testimony

Petitioner Mandy Bangerter is D.B.'s mother. (Tr. 61-62.) She explained that prior to onset of his infantile spasms, D.B. received physical and occupational therapies beginning at two months of age. (Tr. 62-63.) However, she characterized him as doing well and as progressing each week. (*Id*.) D.B. never had any seizures prior to receipt of his six-month vaccinations; however, he did have a history of reacting poorly to vaccinations, including fever, sluggishness, and sleepiness. (Tr. 63.)

The evening of D.B.'s six-month checkup (a Friday), petitioner noticed that as D.B. was waking, "his eyes were kind of like just staring forward." (Tr. 68.) Although she could not recall a specific temperature, petitioner does recall that D.B. did have a "low-grade" fever.[13] (Tr. 67, 69.) This was the only instance of seizure activity

[13] Petitioner stressed that she had a habit and practice, dating back to the infancy of her older child, of giving an initial dose of infant Tylenol upon returning home after vaccinations were administered to prophylactically address anticipated fevers. (Tr. 63-64.) She would then subsequently check for fevers and administer a second dose if a fever was present. (Tr. 86.) When asked how confident she was that she administered an initial dose of Tylenol following D.B.'s six-month vaccinations on February 14, 2014, petitioner testified that there is a "very high probability" that she did based on this habit and practice. (Tr. 85.) She also stressed that D.B. in particular had a history of fevers following vaccinations. (Tr. 86.) Petitioner "would assume" that she administered a second dose of Tylenol on February 14, because she does recall that D.B. had a fever; however, she cannot actually recall whether she did. (Tr. 98.)

petitioner observed that evening. (Tr. 71.) She acknowledged it was subtle, but still felt that something was wrong and told her husband, Jedidiah, that she thought D.B. had a seizure. (Tr. 70-71.) He did not agree at that time. (*Id.*)

The next morning, D.B. exhibited eye rolling as he awoke. (Tr. 72.) At that time he was not yet exhibiting body movement during seizures. (*Id.*) By Saturday evening, his body began to stiffen during the seizures. (*Id.*) By Sunday, movements were still slight, but D.B. was twitching in addition to rolling his eyes. (Tr. 73.) Seizures occurred when D.B. was transitioning from sleeping to waking. (Tr. 73.) Petitioner became confident by Sunday evening that something was happening, because D.B.'s "arms would kind of go out-wise, legs through midline, and his head kind of went rigid and eyes moved." (*Id.*)

By the time D.B. was taken to back to Dr. Leland on Monday, February 17, he was no longer holding his head up and wasn't moving around as much as usual. (Tr. 75.) His eye rolling and body movement during seizures had increased and would result in fatigue.[14] Dr. Leland was able to observe D.B. as he was waking and confirmed that he was experiencing seizure activity. (Tr. 75-76.) Petitioner could not recall whether Dr. Leland referenced any specific term for the seizures, but he did refer them to the children's hospital. (*Id.*)

Petitioner recalled that after onset of his seizures, D.B. could not sit up or roll over. (Tr. 77.) He stopped babbling and cooing and stopped being alert. (*Id.*) "[E]ssentially over time, he had to continue to relearn everything from his therapists and daily work and regiment that was set up." (*Id.*) However, his seizures stopped within 32 days of starting his ACTh treatment. (Tr. 78.) D.B. was starting to sit up again by the end of March. (Tr. 87-89.) By his first birthday, D.B. was able to hold his head up and his gross motor skill issues had resolved; however, petitioner continued to be concerned about his swallowing and difficulty holding a spoon.[15] (Tr. 91-92.) Petitioner also explained, however, that D.B. experienced side effects from the ACTh treatment including extreme weight gain, irritability, and reduced sleep. These symptoms did not cease with the discontinuation of the ACTh and it took several more months for D.B. to return to his normal demeanor. (Tr. 249-50.)

Petitioner indicated that a fever of about 101 degrees would prompt her to administer a second dose of Tylenol. (*Id.*) She testified that the fever she recalls was not concerning at the time. (Tr. 254.) She characterized it as "just a regular fever type pattern that he still gets to this day after receiving something." (*Id.*)

[14] Petitioner struggled to find an appropriate description on this point. She said he was "I don't know – very like tired and exhausted afterwards," but specifically noted that she did not mean lethargic. (Tr. 75.)

[15] During the hearing, respondent's counsel showed petitioner a medical record from March 24, 2014 wherein petitioner is recorded as having reported that D.B. was "back to baseline." (Tr. 87-89 (referencing Ex. 1, p. 71).) Petitioner could not recall what she would have said on that date, but disputed the specific "back to baseline" reference insofar as she recalls D.B. was not back to sitting up by the end of March. (Tr. 89.)

ii. Jedidiah Bangerter's Testimony

Jedidiah Bangerter is D.B.'s father. (Tr. 101.) Mr. Bangerter's testimony is largely in agreement with that of petitioner. He noted that D.B. never had seizures prior to his six-month vaccinations. (Tr. 101.) He was not present for D.B.'s six-month checkup and vaccinations but was with D.B. later that evening. (Tr. 101-03.) He explained that petitioner did raise a concern to him that D.B.'s eyes had begun getting wide and staring off during the evening following his vaccinations, but agrees that he dismissed that concern at the time. (Tr. 102-04.) He also agreed that the condition got progressively worse the following Sunday. (Tr. 106.) Sunday is when Mr. Bangerter also began to become concerned. (*Id*.) Mr. Bangerter indicated that by Monday D.B. had stopped babbling and cooing, was lethargic, and wasn't sitting as well. (Tr. 108-09.) He observed that D.B.'s seizures stopped within a few days of his ACTh treatment and that he has not had a seizure since. (Tr. 109.) He did, however, experience weight gain and irritability caused by the treatment. (*Id*.) D.B. is currently doing well, though he continues to have obstacles. (Tr. 109-10.) Mr. Bangerter testified that D.B. was just returning to babbling and sitting up at his first birthday. He was starting to lose his ACTh-related weight by his first birthday. (Tr. 111-12.)

iii. Robert Leland, M.D.

Dr. Robert Leland, D.B.'s pediatrician, drafted a letter regarding D.B.'s developmental delays. (Ex. 9.) Dr. Leland noted that on the evening subsequent to receiving his routine immunizations, D.B. developed infantile spasms and responded well to ACTh treatment three days thereafter at Children's Hospital Colorado. (Ex. 9, p. 1.) Dr. Leland opined that "[i]t is probable, although it cannot be proven scientifically, that [D.B.], at 6 months after onset of infantile spasms, had additional developmental delays beyond those which would have been associated with his Down's syndrome." (*Id*.) Dr. Leland recommended further consultation from Dr. Francis Hickey.

iv. Sarah Nicholas, MOTR/L

Petitioner also provided a letter from D.B.'s occupational therapist, Sarah Nicholas. (Ex. 8.) In her letter dated April 2, 2016, upon review of her notes from "just before" D.B.'s vaccinations through the date of her letter, Ms. Nicholas indicated that D.B. demonstrated "significant loss in motor skill during my therapy sessions at the time of seizure activity [through] the treatment period for infantile seizures." (Ex. 8, p. 1.) Ms. Nicholas opined that D.B. returned to his skill level prior to onset of seizures around June 5, 2014 and continued to improve slowly with respect to fine motor skills and feeding skills. (*Id.*) Ms. Nicholas stated that D.B. "should have made greater gains, compared to other children [she has] treated with Down syndrome," but that she is "unable to project exactly where he would be had he not had the seizure activity and other medical complications, specifically, reflux." (*Id*.)

During the hearing, Ms. Nicholas discussed her medical records extensively. (Tr. 157-174.) Ms. Nicholas confirmed that D.B. had feeding concerns and reflux prior to the

onset of infantile spasms. (Tr. 157, 178, 185.) She explained that children with Down syndrome are more likely to have choking events because they have low muscle tone and lack coordination. (Tr. 178.) She noted that prior to his infantile spasms, D.B. "clearly had difficulty with coordination and suck, swallow, breath, although not to the degree that he needed a feeding tube." (Tr. 178 (discussing January 30, 2014 record at Exhibit 3, p. 22).) She testified:

> So as I went through these records today and I kind of skimmed over the part about then we went to feeding, feeding and reflux were a significant issue, not that the seizures weren't, but for day-today life, dealing with reflux was very, very difficult for [D.B.]. Feeding aversion and difficulty. And so, I mean, I believed that he – reflux was also in his way of development.

(Tr. 185.)

With respect to developmental trajectory, Ms. Nicholas agreed that there is "wide variability" among individual children and that the developmental gap seen among Down syndrome children compared to other groups widens at about the two-year mark; she stressed, however, that the developmental gap relates to the rate of milestone acquisition rather than the order of developmental milestones that are achieved. (Tr. 179-81.) With regard to D.B., she agreed that he showed gains beyond his pre-seizure level of development within five months of the end of his seizures. (Tr. 186.) However, she testified that D.B. "had a period of months where he was not performing to the level he was prior to the seizure, and then he started making gains again. But certainly, I think if we had had those months, he would have been further along at this point, at the end of October[.]" (Tr. 175.) Asked if she could attribute any of D.B.'s developmental delays after June of 2014 to D.B.'s infantile spasms, she stated "I can't point to anything specific. I felt that he would have been further along in his development at his current rate of development prior to the seizures compared to his rate of development after the seizures." (Tr. 186.)

IV. Expert Opinions

a. Petitioner's Experts

i. Karen Harum, M.D.

Additionally, petitioner presented an opinion from Dr. Karen Harum from Clinic for Special Children. (ECF No. 40; Ex. 12.) Dr. Harum is a neurodevelopmental pediatrician at the Clinic for Special Children in Wilmington, North Carolina. Previously she was a clinical assistant professor in the department of pediatrics at Eastern Carolina School of Medicine and, before that, an instructor of neurology and developmental pediatrics at the Kennedy Krieger Institute at Johns Hopkins University School of Medicine. (Ex. 13, p. 1.) Dr. Harum obtained her medical degree at the University of Miami School of Medicine in 1987 and completed a fellowship in neurodevelopmental pediatrics at the Kennedy Krieger Institute. (*Id*. at 2.) She is board certified in neurodevelopmental disabilities by the American Board of Pediatrics. (*Id*. at

3.) She was accepted without objection as an expert in pediatrics with a specialty in pediatric development.[16] (Tr. 7-8.)

Regarding whether D.B. experienced residual effects following his recovery, Dr. Harum opined that D.B.'s developmental progress was negatively affected for more than six months after the onset of his infantile seizures. (Ex. 12, p. 1.) Using developmental quotients (DQ) to measure his developmental progress in the areas of fine motor, gross motor, and feeding skills, Dr. Harum indicated that D.B.'s scores were dropping over time, even accounting for Down syndrome as an impediment. (*Id*. at 1.) She explained that DQ "are calculated as a ratio of the age equivalent of the relevant skill, over the actual age of the child." (Ex. 15, p. 1.) From the records, Dr. Harum summarized that at 6.5 months, D.B.'s DQ was 77 in gross motor skills and 61 in fine motor skills, and at 16 months, his DQs were 37 and less than 50. (Ex. 15, p. 2.) From that information, Dr. Harum opined that D.B. continued to decline for more than six months following his injury and he did not entirely recover to his baseline before the onset of his seizures until about 42 months of age. (*Id*.)

Dr. Harum opined that considering D.B.'s Down syndrome, his recovery should not have lasted more than 12 months, and he should have returned to achieving DQ levels at 60-77 by 19 months, not 42. (Ex. 15, p. 2.) Moreover, "developmental abilities between infancy and two years of age are not expected to be greatly different between typically developing children and children with DS." (Ex. 16, p. 2.) Yet, Dr. Harum also opined that D.B. was following the developmental trajectory for children with Down syndrome aside from the residual deficits in hand ability and feeding difficulty. (*Id*. at 3.) Specifically, she opined:

> Putting into perspective the somewhat typical developmental trajectory for Down syndrome, it appears that DB is not markedly different from his [Down syndrome] peers, yet he is left with residual deficits in L hand ability and in oropharyngeal motor skills that affect his feeding in a pervasive way.
>
> From these data, we can therefore surmise that DB suffered residual effects of the alleged injury for >6 months.

(Ex. 16, p. 3.)

During the hearing, Dr. Harum testified in accordance with her reports. (Tr. 5-59.) Critically, however, for the few developmental quotients Dr. Harum calculated for 6.5, 8, 10, and 16 months, she did not disclose in her report the basis for those calculations. (Ex. 16, p. 2.) During the hearing, she was not able to explain the basis for those calculations. (Tr. 33.) Because D.B. suffered his infantile spasms at about six

[16] Of note, however, although Dr. Harum stressed that she has a strong background in neurology and neuroscience, when asked if she has ever practiced as a neurologist, she indicated "not as you conceive of neurology, no." (Tr. 21.)

months of age, these calculations served as the baseline premise for her entire opinion regarding D.B.'s developmental trajectory.

ii. Marcel Kinsbourne, M.D.

With respect to causation, petitioner presented an expert opinion by neurologist Marcel Kinsbourne, M.D. Dr. Kinsbourne served as a senior fellow at the Center for the Study of Aging and Human Development at Duke University, an adjunct professor of neurology at Boston University School of Medicine, a research professor at the Center for Cognitive Studies at Tufts University, and a professor of psychology at New School University. (Ex. 23.) Dr. Kinsbourne obtained his B.M.B. Ch. from Oxford University Medical School in 1955 and his medical degree from State of North Carolina in 1967. Dr. Kinsbourne has published over 400 medical articles. Dr. Kinsbourne was accepted without objection as an expert in pediatric neurology. (Tr. 117.)

Beginning with his second report,[17] Dr. Kinsbourne addressed the question of whether D.B.'s DTaP vaccination caused or triggered the onset of his infantile spasms. (Ex. 24.) First, Dr. Kinsbourne opined that findings from the National Childhood Encephalopathy Study (NCES) as later published by Bellman et al., support the idea that the diphtheria, tetanus, and whole cell pertussis ("DTP") vaccine can trigger onset of infantile spasms within 6 days. (Ex. 24, p. 1 (citing Bellman et al., *Infantile Spasms and Pertussis Immunisation,* The Lancet, 1031-34 (1983) (Ex. 28.)) He also cited an earlier study by Melchior which he also suggests demonstrated an association between onset of infantile spasms and DPT. (*Id*. (Melchior, *Infantile spasms and early immunization against whooping cough: Danish survey from 1970-1975,* 52 ARCHIVES OF DISEASE IN CHILDHOOD 137-37 (1977) (Ex. 34.)) Dr. Kinsbourne opined that D.B. had cryptogenic infantile spasms, reporting that Bellman found children with cryptogenic infantile spasms who received DPT vaccinations had more seizure onsets within the first week. (Ex. 24, p. 2 (citing Bellman et al., *supra,* at Ex. 28).) Additionally, Dr. Kinsbourne believed that a later onset of spasms would result in milder developmental delays. (*Id*. at 2 (citing Arya et al., *Epilepsy in children with Down syndrome,* 13(1) EPILEPTIC DISORD. 1-7 (2011) (Ex. 25.)) Although the vaccination at issue is DTaP (acellular pertussis) and not DTP, Dr. Kinsbourne suggests that the mechanism is similar and the pertussis toxin promotes proinflammatory cytokine output that triggers seizures. (*Id*. at 3.) Relatedly, "[c]hildren with Down syndrome have been reported to have cytokine excess in blood and brain." (*Id*.)

[17] Dr. Kinsbourne's first report did not discuss vaccine causation. (Ex. 20.) Rather, it focused exclusively on D.B.'s medical history and whether his infantile spasms had any lasting effect on his development beyond the six-month mark. (*Id*.) However, during the hearing, Dr. Kinsbourne later deferred to Dr. Harum's opinion with respect to D.B.'s developmental course. (Tr. 236, 238.) On the question of residual consequences, Dr. Kinsbourne explained in that first report that the adverse impact of infantile spasms on child development depends on the duration of the spasms and subsequent treatment. (Ex. 20.) Moreover, children with Down syndrome usually responds well to ACTh treatment, "[t]hat does mean, however, that the developmental setback that Down syndrome children incur when they have had infantile spasms is so readily compensated." (Ex. 20, p. 2.) Using the DQs as summarized by Dr. Harum, Dr. Kinsbourne is also of the opinion that the residual effects of the alleged vaccine injury lasted more than six months. (*Id*. at 3.)

Second, Dr. Kinsbourne cited a theory for the mechanism of injury explored by Baram and Hatalski, which he contended demonstrates developmental seizures, including infantile spasms, can be provoked by injurious or stressful stimuli affecting neuronal excitability via the release of corticotropin releasing hormone ("CRH").[18] (*Id*. at 2; Ex. 40, pp. 3-4.) Dr. Kinsbourne opined that D.B. had a lower threshold for seizures due to his Down syndrome and was "predisposed to react adversely to potentially excitatory influences." (Ex. 24, pp. 2-3.) Dr. Kinsbourne stated:

> The development of Down syndrome changes in the brain, which is prenatal, bestows a susceptibility to infantile spasms. Because this seizure variant is age-dependent, when the brain has developed to the point that neuronal circuitry can create spasms and hypsarrhythmia, the clinical onset of the spasms can be triggered by immediately preceding events in the already susceptible infant when s/he is within the applicable age range, usually cited as being three to eight months.

(*Id*. at 2.)

Dr. Kinsbourne proposed that vaccinations activate the Toll-like receptors of the innate immune system that would release cytokines that then trigger the seizures. (*Id*. at 3-4.) He also noted that this process can be rapid and related that DTaP vaccinations can trigger adverse reactions within the first 24 hours after administration. (*Id*. at 4.) Thus, Dr. Kinsbourne opined that D.B.'s susceptibility to infantile spasms was a first hit and the DTaP vaccination, acting as a trigger, was the second hit that resulted in the onset of infantile spasms. (Ex. 40, pp. 2-3; Ex. 49, p. 2.) Dr. Kinsbourne opined that both the immune response to vaccination and the stress associated with injection would act on the endocrine system to elevate CRH consistent with the Baram hypothesis. (Ex. 40, p. 4; Tr. 152-53 (discussing Jansen et al., *Cortisol reactivity in young infants,*35 PSYCHONEUROENDOCRINOLOGY 329-38 (2010) (Ex. 86.))

During the hearing, Dr. Kinsbourne largely testified in accordance with his prior reports (Tr. 115-240); however, he also introduced for the first time the alternative suggestion that what D.B. initially suffered was not infantile spasms, but tonic/partial seizures. (Tr. 123-24, 220-21 (citing Carrazana et al., *Facilitation of Infantile Spasms by Partial Seizures,* 34(1) EPILEPSIA 97-109 (1993) (Ex. 92.)) He opined that it was these seizures, rather than D.B.'s infantile spasms, that were vaccine-caused via proinflammatory cytokines. (Tr. 135-37, 221-22.) He further opined that these initial seizures transformed into infantile spasms.[19] (Tr. 135-37.)

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[18] Petitioner filed two papers by Dr. Tallie Baram. Baram and Hatalski, *Neuropeptide-mediated excitability: a key triggering mechanism or seizure generation in the developing brain*, 21(11) TRENDS NEUROSCI. 471-76 (1998) (filed as Exhibits 26, 41, 63, and 76); Baram, et al, 31(5) *Corticotropin-releasing Hormone – induced Seizures in Infant Rates Originate in the Amygdala*, ANN NEUROL. 488-94 (1992) (filed as Exhibit 89).

[19] While discussing the Carrazana paper (Ex. 92), which he testified represented "exactly what happened with [D.B.]," Dr. Kinsbourne testified that "the vaccines surely triggered the partial seizures, *not the infantile spasms*." (Tr. 136 (emphasis added).) This would actually seem to represent a retraction of

b. Respondent's Expert: Gregory Holmes, M.D., Ph.D.

Respondent provided a responsive report from Gregory Holmes, M.D. Dr. Holmes is board certified in pediatrics, clinical neurophysiology, and psychiatry and neurology with special qualification in child neurology. (Ex. B, p. 2.) Dr. Holmes currently holds a teaching and chair position at the University of Vermont College of Medicine as well as being a physician leader of neurology at the University of Vermont Medical Center. (Ex. B, p. 1.) He obtained his medical degree from the University of Virginia School of Medicine in 1974. (*Id*.) Like Dr. Kinsbourne, his curriculum vitae lists hundreds of publications. (Ex. B.) Dr. Holmes was presented as an expert in pediatric neurology with an additional specialty in seizure disorders; however, petitioner objected to the designation of this specialty.[20] (Tr. 268-69.)

Citing to the Institute of Medicine, Dr. Holmes stated that there is no evidence to support the notion that DTaP vaccination causes infantile spasms. (Ex. A, p. 10 (citing the IOM report).) Similar to Dr. Kinsbourne, Dr. Holmes cited the prevalence of seizures in patients with Down syndrome (1-13% for individuals with DS versus 1.5-5% for the general population). (Ex. A, p. 9.) Dr. Holmes also noted that children with Down syndrome and infantile spasms typically respond well to treatment and prompt treatment results in better prognosis. (*Id*.) For infantile spasms to occur, there's no need for a trigger. (Ex. C, p. 3.) Therefore, D.B. had symptomatic infantile spasms that were consistent with his Down syndrome, not cryptogenic infantile spasms.[21] (Ex. C, p. 2.)

According to Dr. Holmes, none of the studies Dr. Kinsbourne cited supports a relationship between vaccination and infantile spasms with developmental delay. (Ex. A, p. 11.) Additionally, there is no evidence that onset of infantile spasms later in life reduces the developmental impact. (*Id*. at 11.) Dr. Holmes added that the materials Dr. Kinsbourne relied on focused on DTP vaccinations while D.B. received the DTaP vaccination, which is less reactogenic. (*Id*.) He insisted that relying on literature referring to DTP vaccines rather than DTaP from 30 years ago is neither helpful nor relevant. (Ex. D, p. 2.) Additionally, there is no evidence that DTaP vaccination causes

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substantial portions of Dr. Kinsbourne's prior reports and likely represents a veiled acknowledgement of the fact that much of the evidence petitioner relies on that is specific to the modern acellular DTaP vaccine (as opposed to the older whole cell DPT vaccine) relates to unitary post-vaccination seizures rather than the specific seizure disorder of infantile spasms. For purposes of this decision, however, I treat the direct causation of infantile spasms by vaccination and the indirect causation of infantile spasms via partial seizures as theories presented in the alternative.

[20] That objection is addressed in detail below in section V(d) and found to be unpersuasive.

[21] Dr. Kinsbourne first opined that D.B.'s infantile spasms were cryptogenic, meaning of obscure or unknown origin. (Ex. C, p. 2.) And although Dr. Holmes explained why he does not think the infantile spasms are cryptogenic, he explained that categorizing the infantile spasms as cryptogenic does not dictate outcome but only etiology, and here, "[w]hether one calls these idiopathic, cryptogenic, or symptomatic is irrelevant in this case." (*Id*.)

infantile spasms through proinflammatory cascades or activation of cytokines.[22] (Ex. D, p. 3.) Regarding Dr. Kinsbourne's two hit theory, Dr. Holmes stated that the medical records do not support that D.B. had a slow development of susceptibility to infantile spasms "that resulted in an 'explosive reaction' to the DTaP vaccine." (Ex. C, p. 2.)

Additionally, Dr. Holmes opined that it is not biologically possible for onset of infantile spasms to occur within 12 hours after vaccination. (*Id*. at 12.) Dr. Holmes emphasized that the "interval between brain injury and the onset of infantile spasms ranges from 6 weeks to 11 months." (*Id*.) Dr. Holmes also stressed that there is "no evidence that a later onset of infantile spasms the better the outcome," stating that the articles cited by Dr. Kinsbourne do not support this contention. (Ex. C, p. 2.) Moreover, Dr. Holmes asserted that even accepting petitioner's theory that a vaccine can trigger infantile spasms in a predisposed child, there is no evidence predicting any effect on outcome. (Ex. D, p. 2.)

Dr. Holmes also noted that, on review of the records, D.B. did not have any adverse reactions to his first and second DTaP vaccinations and that D.B. was not developing normally prior to the vaccination at issue. (Ex. A, pp. 2-3, Ex. D, p. 2.) Additionally, the records indicated that D.B.'s spasms ceased in early March after ACTh treatment and he regained certain skills. (Ex. A, p. 7.) Thus, Dr. Holmes concluded that D.B. returned to baseline within a month of ACTh treatment and that his developmental delays thereafter were consistent with his Down syndrome. (*Id*. at 9.) Dr. Holmes opined that the developmental regression that occurred once D.B. recovered, as evidenced in his EEG, cannot be linked to the infantile spasms, but that D.B. had other chronic problems that contributed to his developmental issues. (*Id*. at 13.) Specifically, he stated:

> While it is clearly recognized that cognitive regression can occur with infantile spasms in Down syndrome, the developmental regression that occurred following the end of hypsarrhythmia and infantile spasms obviously cannot be attributed to the infantile spasms. Even if there was permanent damage following the short period of infantile spasms and hypsarrhythmia, this would not explain the decline months following remission of the condition. Dr. Kinsbourne does not provide an explanation for why [D.B.] should decline following the cessation of infantile spasms.

(Ex. C, p. 3.) Dr. Holmes also testified in accordance with his written reports. (Tr. 261-354.)

[22] Dr. Holmes provided an alternative mechanism, discussing the **$GABA_BR$**-mediated mechanism. (Ex. A, p. 12.)

V. Discussion

a. *Althen* Prong One

Under *Althen* prong one, petitioners must provide a "reputable medical theory," demonstrating that the vaccine received can cause the type of injury alleged. *Pafford v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1355–56 (Fed. Cir. 2006) (citations omitted). To satisfy this prong, petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). Such a theory must only be "legally probable, not medically or scientifically certain." *Id.* at 549. However, petitioners may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1378-79 (Fed. Cir. 2009) (citing *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1325-26 (Fed. Cir. 2006)).

There is no dispute in this case that the DTaP vaccine can cause seizures in some contexts.[23] (Tr. 118 (Kinsbourne); Tr. 344-45 (Holmes).) However, that is not the question at issue in this case. The condition at issue in this case is not interchangeable with other forms of epilepsy or seizure activity. D.B. suffered a specific seizure disorder known as infantile spasms, the diagnosis of which is not disputed. And while Dr. Holmes agrees on respondent's behalf that a single seizure can be vaccine-caused, he disagrees that vaccines cause any form of epilepsy and further stresses that infantile spasms in particular are not "provoked" seizures. (Tr. 294-96; 344-45.)

The condition of "infantile spasms" (also referred to as epileptic spasms or "West Syndrome") represents an epileptic[24] encephalopathy.[25] (Lee & Ong, *Epidemiology of*

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[23] Dr. Holmes agreed that DTaP can cause febrile seizures, but disagreed that DTaP has been shown to cause afebrile seizures. (Tr. 344-45.) In fact, while he agreed that vaccination in general can cause febrile seizures, he noted that the question of whether they can cause afebrile seizures is generally considered contentious. (*Id.*) In this case, petitioner has also filed a package insert for the DAPTACEL vaccine, a DTaP vaccine manufactured by Sanofi Pasteur, that includes seizures occurring within three days of vaccination as adverse reactions to the vaccine. (DAPTACEL package insert, *supra,* at Ex. 55.) There is no evidence of record to indicate that D.B. was administered the DAPTACEL vaccine specifically; however, for more detailed discussion of the DAPTACEL package insert, see n. 33, *infra*.

[24] An epilepsy is "any of a group of syndromes characterized by paroxysmal transient disturbances of the brain function that may be manifested as episodic impairment or loss of consciousness, abnormal motor phenomena, psychic or sensory disturbances, or perturbation of the autonomic nervous system. A single episode is called a seizure (q.v.). Many types of epilepsy are combinations of different kinds of seizures. Epilepsy is classified as either symptomatic or idiopathic according to whether the cause is known or unknown. Both of these types may be further subdivided into partial and generalized types depending on whether the seizures begin with localized, limited brain dysfunction or with widespread brain dysfunction." *Epilepsy*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=16869 (last visited Jan. 11, 2022).

[25] Broadly speaking, encephalopathy is defined as "any degenerative disease of the brain." *Encephalopathy*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=16202 (last visited Jan. 11, 2022).

West syndrome in Singapore, 23 BRAIN & DEV. 584-85, 584 (2001) (Ex. A, Tab 15); Ogawa, et al., *Cytotoxic edema at onset in West syndrome of unknown etiology: A longitudinal diffusion tensor imaging study,* 59(2) EPILEPSIA 1-21, 1 (2018) (Ex. 43.)) Outwardly, it is characterized by "repetitive bursts of myoclonic[26] jerking of the head or limbs." (Bellman et al., *supra*, at Ex. 28, p. 1031.) However, the three cardinal features of infantile spasms are: (1) encephalopathy; (2) epileptic spasms; and (3) hypsarrhythmia. (Lee & Ong, *supra,* at Ex. A, Tab 15, p. 584; Ogawa et al., *supra,* at Ex. 43, p. 1.) Infantile spasms are considered an age-dependent condition typically occurring within the first year of life, most often between six to eight months of age. (Osbourne et al., *The underlying etiology of infantile spasms (West syndrome): Information from the United Kingdom Infantile Spasms Study (UKISS) on contemporary causes of their classification,* 51(10) Epilepsia 1-28, 2 (2010) (Ex. 48); Arya et al., *supra,* at Ex. 25, p. 2.) Children with Down syndrome, like D.B., are more likely than the general population to suffer epilepsies in general and infantile spasms is the most common epilepsy among children with Down syndrome. (Arya et al., *supra,* at Ex. 25, pp. 1-2.) The expert testimony in this case indicates that it is the hypsarrhythmia underlying the condition – a key characteristic of infantile spams that can be clinically silent apart from detection on EEG – that is primarily responsible for any lasting damage. (Tr. 128-29, 235 (Dr. Kinsbourne); Tr. 272-78 (Dr. Holmes).)

In this case, Dr. Kinsbourne's opinion suggests two different inquiries. First, Dr. Kinsbourne is clearly of the view that there is evidence directly suggesting that certain vaccines, including whole cell pertussis and diphtheria/tetanus vaccines, can trigger the onset of infantile spasms. Second, Dr. Kinsbourne opines that infantile spasms can be circumstantially evidenced as being vaccine-caused, either directly or via a partial seizure. He indicates that in this case D.B. suffered an initial, vaccine-caused, partial/tonic seizure that in turn developed into infantile spasms, thereby theorizing an indirect causal relationship between vaccination and infantile spasms. On the whole, Dr. Holmes is far more persuasive than Dr. Kinsbourne and petitioner has not met her burden under *Althen* prong one under either theoretical approach.

i. <u>Older literature is unpersuasive in suggesting any association between vaccines and the development or onset of infantile spasms</u>

First, Dr. Kinsbourne is not persuasive in arguing that the medical literature supports any association between the DTaP vaccination and infantile spasms. The evidence he principally relies upon – two studies from the 1970's and early 1980's by Melchior and Bellman respectively - are old and equivocal, presenting only very weak evidence. (*See* Melchior, *supra,* at Ex. 34; Bellman et al., *supra,* at Ex. 28; Tr. 137-40.)

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[26] "Myoclonus" refers to "shocklike contractions of a portion of a muscle, an entire muscle, or a group of muscles, restricted to one area of the body or appearing synchronously or asynchronously in several areas. It may be part of a disease process (e.g., epileptic or post-anoxic myoclonus) or be a normal physiologic response (e.g., nocturnal myoclonus)." *Myoclonus*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=32802 (last visited Jan. 11, 2022).

More recent literature filed by Dr. Holmes refutes these older studies. To understand why these older studies are not persuasive, it is worth discussing them at length.

According to the literature filed in this case, a possible link between pertussis vaccination and infantile spasms was first proposed in 1964. (Melchior, *supra*, 34, p. 1.) However, subsequent papers suggested that the possible association was merely a coincidence of timing. (*Id*.) In April of 1970, Denmark changed its immunization schedule for pertussis vaccination. Previously, the pertussis vaccine was typically administered in Denmark as a triple combination at five, six, and 15 months of age. After April of 1970, that schedule was advanced so that pertussis was administered as a monovalent vaccine at five and nine weeks of age and then again at 10 months. (*Id*.) However, immunization against diphtheria-tetanus-polio was still given at five, six and 15 months of age. (*Id*.) This provided an opportunity to examine whether the change in the vaccine schedule would result in a statistically significant change in the typical age of onset for infantile spasms. (*Id*.) J.C. Melchior published a survey study regarding this question in the Archives of Disease in Childhood in 1977. (*Id.*)

Melchior compared 113 cases of infantile spasms diagnosed between April 1 of 1970 and March 31 of 1975 to 86 cases of infantile spasms occurring from 1957 to 1967. (Melchior, *supra*, at Ex. 34, p. 1.) Of the 113 cases from the early 1970's, 40 were classified as cryptogenic, 60 of the subjects as symptomatic, and the remaining 13 reported as having an unclear etiology, but with immunization occurring prior to onset. (*Id*. at 2.) Of those 13 subjects, six had seizures following either the first or second dose of monovalent pertussis and seven had seizures following a combined diphtheria, tetanus, and polio vaccination. (*Id*. (Table 2).) The conclusion reached by the study was that: "A comparison of the age of onset of infantile spasms shows no significant difference between the series of spasms before the new immunization programme and after." (*Id*. at 2.)

Despite these conclusions, Dr. Kinsbourne pointed out certain findings specific to the pertussis vaccine. He noted that the Melchior study results demonstrate that:

> 12% of cases of infantile spasms had onset before age 2 months when DTP had not yet been given by then, whereas 23% began before the child was two months old when DTP had been given at 5 weeks. Melchior did not take advantage of this opportunity to analyze the differential outcomes at age two months statistically. He only compared the final outcomes of the two subgroups, which did not differ significantly.[27]

(Ex. 24, p. 2.)

Notably, however, Melchior did at least broadly address the concern raised by Dr. Kinsbourne, explaining that if the pertussis component of the vaccine was isolated

[27] Although Dr. Kinsbourne references the vaccination at issue in Melchior as "DPT," Melchior indicates that the post-1970 vaccination schedule changed to administration of a monovalent pertussis vaccination. (Melchior, *supra,* at Ex. 34, p. 1.)

as an etiologic factor, one would expect to see *both* an increase in incidence of infantile spasms in the younger group *and* a decrease among the older group. (*Id*. at 2-3.) But this was not observed in the data. Melchior noted that:

> [o]f special interest is the occurrence of infantile spasms in 7 children, developing within 2 weeks of the diphtheria-tetanus-polio immunization. This seems to confirm the opinion that we are dealing mainly with a time-coincidence and suggests that whatever immunization we administer in the age groups between 1 and 2 months and 9 and 10 months, some children will develop neurological disorders which are typically associated with these age groups.

(Melchior, *supra*, at Ex. 34, p. 3.) Melchior characterized the possibility of a causal connection between pertussis vaccination and infantile spasms as "very unlikely." (*Id*.) A figure from the study illustrates the point:

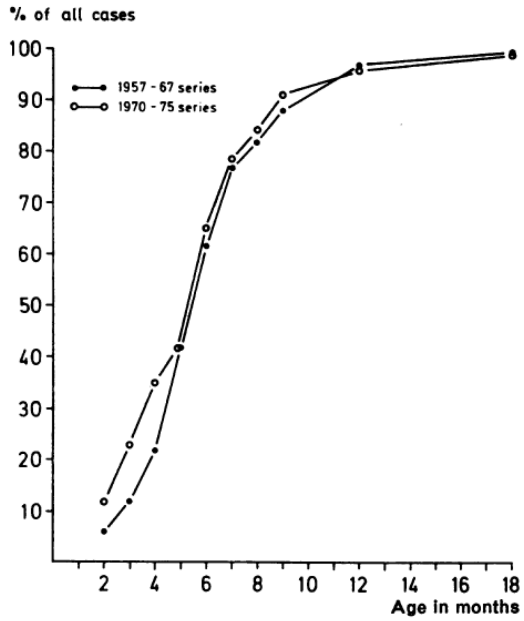

Fig. *Comparison between age at onset of infantile spasms in two Danish series after different immunization programmes. The graphs show for each series the cumulative percentage of infants in the series who had started having infantile spasm at each age.*

(*Id*. at 2.) Even while the increase at two months observed by Dr. Kinsbourne is visible, this figure still shows that the overall distribution of onset of infantile spasms remained substantially the same before and after the change in Denmark's vaccination schedule. Moreover, onset at 6-8 months of age among the 1970 series remained slightly above the 1957 series even after pertussis was no longer administered at six months of age.

Subsequently, in 1983, Bellman et al., published a further study of 269 cases of infantile spasms reported to the National Childhood Encephalopathy Study ("NCES") in

Great Britain. (Bellman et al., *supra*, at Ex. 28, p. 1031.) Of those, 92 were classified as symptomatic, 163 as cryptogenic, and a further 14 as "doubtful." (*Id*.) Bellman compared the immunized population to age-matched controls. (*Id*. at 1032.) Bellman examined not only the DTP vaccine, but also a DT vaccine without any pertussis at all. (*Id*.) Examining the pertussis vaccine, the Bellman study found no significant association between spasms and the administration of a pertussis vaccine in either the prior seven days or 28 days. (Bellman et al., *supra*, at Ex. 28, p. 1033.) However, they did find that:

> a small excess in the number of cases over that expected by comparison with controls in 7 days after immunization with both DTP and DT vaccines followed by a corresponding deficit in the next 3 weeks suggests that, in some cases, immunization may trigger the onset of spasms or attract attention to symptoms in children destined to show the condition overtly within a short time.

(*Id*.) The authors allowed that the small excess in cases within seven days might speak to vaccination being a "trigger" of spasms, but also indicated that it may be due to the fact of vaccination attracting greater attention to symptoms displayed by children destined to show the condition more overtly in a short time. (*Id.*) The latter explanation was viewed as being in harmony with the prior Melchior study. (*Id*.)

In his second report, Dr. Kinsbourne sought to emphasize the "trigger" aspect of the Bellman findings while waving away the Bellman study's overall conclusion as to the lack of any causal association as an "intuition as to destiny that cannot be tested." (Ex. 24, p. 2.) However, the Bellman data was revisited in 1998 by Goodman et al. (Goodman et al., *Temporal relationship modeling: DTP or DT immunizations and infantile spasms,* 16(2/3) VACCINE 225-31 (1998) (Ex. A, Tab 18.)) The points stressed by Goodman reveal this to be disingenuous. In the 1998 Goodman et al. follow up, the authors cautioned against reading too much into the term "triggered." They explained that subsequent to the NCES, the U.S. Institute of Medicine ("IOM")[28] had conducted its own evaluation of the available data, including review of the Bellman data, and rejected any causal association between DTP and infantile spasms. (Goodman et al., *supra,* at Ex. A, Tab 18, p. 226.) They agreed with that conclusion. (*Id*. at 5-6.) To further clarify the issue in light of the subsequent commentary, Goodman et al., reexamined the Bellman data using three different statistical models – association (asking whether the overall frequency of infantile spasms increases post-vaccination), temporal shift (asking whether administration of a vaccine changes the timing of onset without necessarily

[28] The Institute of Medicine (known as the National Academy of Medicine since 2015) is the medical arm of the National Academy of Sciences. The National Academy of Sciences ("NAS") was created by Congress in 1863 to be an advisor to the federal government on scientific and technical matters (*see* An Act to Incorporate the National Academy of Sciences, ch. 111, 12 Stat. 806 (1863)), and the Institute of Medicine is an offshoot of the NAS established in 1970 to provide advice concerning medical issues. When it enacted the Vaccine Act in 1986, Congress directed that the IOM conduct studies concerning potential causal relationships between vaccines and illnesses. *See* § 300aa–1 note.

changing the overall frequency), and no-effect (asking how the studied period compares to the expected rate). (Ex A, Tab 18, p. 1.)

The Goodman authors stressed that, consistent with the prior use of the term "triggered" in Bellman, only the temporal shift model suggested any significant signal.[29] Because they specifically demonstrated that the associational model showed no significant increase in cases of infantile spasms following vaccination, they cautioned against any understanding of the term "trigger" to imply an association between vaccination and infantile spasms. (*Id.* at 4-5.) The temporal shift among the "previously normal" group was statistically significant, meaning that the cases demonstrated a "significant" fit to the temporal shift model. (*Id.*) Nonetheless, the authors also explained that "[t]he no effect model appears to be the *best fitting* of the three models for the entire group of those with DTP or DT exposure." (*Id*. (emphasis added).) This means that "[t]here are no more immunizations given in the month prior to seizure onset than would be expected." (*Id*. at 6.) Thus, the authors reiterated the caution first included in the Bellman article that the observed temporal shift may be due to increased attention to symptoms. Specifically, they noted: "[a] temporal association with immunization may be sought by parents for children who have no other apparent antecedent factor for infantile spasms," thus, "a fit to the temporal shift model for previously normal cases may reflect a social or perceptual temporal shift, a biological temporal shift, or a combination of both processes." (*Id*.) The authors also cautioned that the insidiousness of onset for infantile spasms makes it difficult to identify a precise date of onset. (*Id*.)

Petitioner also relies on a 2011 retrospective analysis of vaccine-related seizures conducted by von Spiczak et al., using the national German database of adverse events following immunization. (von Spiczak, *supra,* at Ex. 36.) The authors indicated that the risk for epilepsy following DTaP vaccination is not elevated, but noted instances where epilepsy presents with its first seizure post-vaccination. (*Id*. at 2.) In their own review, the authors gathered a cohort of 17 cases of infantile spasms, 10 of which were apparently cryptogenic. (*Id*. at 10.) Among these subjects, they observed that for nine out of the 17 their first seizure was "associated with the vaccination." (*Id*. at 8.) They noted that their findings may be consistent with the temporal shift observed in Goodman but stressed that their study design did not test that hypothesis. (*Id*. at 10.) Thus, the von Spiczak paper does not provide any further support for Goodman's temporal shift or serve to extend the Goodman findings to the DTaP vaccine at issue in this case. In fact, citing both the Goodman study (discussed above) and Guggenheim study (discussed below), von Spiczak explained that any causal relationship remains controversial. (*Id*.) Additionally, Dr. Holmes was highly critical of this study for not having any control group or disclosing the overall population. Based on his own assumptions as to the relevant population, he estimates that it is likely these results

[29] Only the results for the "previously normal" group demonstrated a temporal shift compared to controls during the first week prior to vaccination as compared to the preceding three weeks. (*Id.*) When examining the entire group of infantile spasm subjects against controls, Goodman explained that "[a]s the odds ratio for the first week prior to seizure onset is not significantly greater than that for the subsequent three weeks, there is no evidence for a fit to the temporal shift model." (*Id*. at 5.)

would demonstrate an "extremely low" likelihood of vaccine-associated infantile spasms. (Tr. 307-08.)

Dr. Holmes also stresses that this issue was also examined by the Institute of Medicine in 2012. (Ex. A, p. 10 (citing Committee to Review Adverse Effects of Vaccines, Institute of Medicine, Stratton et al., *Diphtheria Toxoid--, Tetanus Toxoid--, and Acellular Pertussis—Containing Vaccines, in* ADVERSE EFFECTS OF VACCINES: EVIDENCE AND CAUSALITY 525-97 (2011) (Ex. A, Tab 14.)) With respect to the specific condition of infantile spasms and vaccinations containing tetanus and/or diphtheria toxoids, the IOM committee reported three studies, the Goodman study discussed above, the sole epidemiologic study examined, and a 1983 study by Pollock and Morris and a 1996 study by Schmitt, both considered as potential mechanistic evidence. (IOM, *supra,* Ex. A, Tab 14, pp. 537-38.) The committee was critical of the Goodman study as lacking validity and precision to assess an association. In particular they were critical of the study for not disclosing how control subjects were selected. They concluded that the weight of epidemiologic evidence was insufficient or absent to assess any association between infantile spasms and either diphtheria or tetanus toxoided vaccines or acellular pertussis vaccines. (*Id*. at 538.) The committee's discussion of Pollock and Morris and Schmitt is limited to noting that they did not provide evidence beyond temporality and these studies are not otherwise a part of the record of this case. Ultimately, the committee concluded that the evidence is inadequate to accept or reject a causal relationship. (*Id*. at 539.)

In his reports and during the hearing, Dr. Kinsbourne contended that the IOM's conclusion lacks value, because "[p]itching the selection criterion so high is appropriate if one wishes to construct a 'definitive picture.' But that is far from the standard or goal in Vaccine Court proceedings." (Ex. 40, p. 1.) During the hearing, he characterized the IOM's report as "seriously irrelevant." (Tr. 241-43.) In this case, the IOM examined the Goodman study, which reviewed the same data as the Bellman study relied upon by Dr. Kinsbourne, and concluded that, although it did contribute to the weight of epidemiologic evidence, the study had flaws. That Dr. Kinsbourne disagrees with that criticism does not automatically render it overly stringent.[30] In any event, the Goodman study has

[30] Dr. Kinsbourne is correct to the extent that special masters are not bound by the IOM's conclusions and it has been previously observed, as Dr. Kinsbourne suggests, that the IOM employs a standard for finding causation that is higher than what is required by petitioner's burden of proof. *E.g. Raymo v. Sec'y of Health & Human Servs.*, No. 11-654V, 2014 WL 1092274, at *21, n.39 (Fed. Cl. Spec. Mstr. Feb. 24, 2014). Accordingly, IOM reports and findings should be approached with caution. However, his further characterization of the report as "seriously irrelevant" based on the preponderant evidence standard goes too far. First, the question is not whether the IOM itself employs a preponderant standard, but whether the investigation and conclusions reflect reasonable medical and scientific rigor. Dr. Kinsbourne's own challenge to the quality of the IOM's investigation must be weighed against Dr. Holmes's competing endorsement and the IOM should not be expected to cater specifically to this Program's burden of proof any more than the authors of any other study or article that includes a retrospective literature review. Second, special masters apply the preponderant evidence standard to the record as a whole, not specific pieces of evidence in isolation. The IOM report is not dispositive, but nor does it need to be dispositive to constitute relevant evidence that must be evaluated in reaching a determination based on the record as a whole. Numerous prior cases have demonstrated that special masters may account for IOM findings in reaching their decisions. *See, e.g., Crutchfield v. Sec'y Health & Human Servs.*, 125 Fed. Cl. 251, 262

been separately filed into the record of this case and I have reached my own conclusion as to its weight. During the hearing I also asked Dr. Kinsbourne whether he knew the IOM's literature review to be in any way deficient. That is, I invited Dr. Kinsbourne to draw my attention to any study he is aware of that was overlooked by the IOM in reaching its conclusion. However, he indicated he had not considered that issue and could not answer.[31] (*Id*.)

Standing alone, the findings from Melchior and Bellman do not provide significant support for Dr. Kinsbourne's causal opinion. While Bellman noted a small clustering of cases within one week of vaccination, the overall result did not support a causal relationship. Moreover, Dr. Kinsbourne is not persuasive in citing only a subset of data from Melchior to reach the opposite conclusion as the study author. Thus, the overall findings of these studies weigh against the conclusion that there is any causal relationship between vaccination and infantile spasms. Nonetheless, Dr. Kinsbourne cites Bellman et al., for the proposition that the DPT vaccine was shown to "trigger" clinical onset of infantile spams, referring to it as "a trigger which changed the

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(2014) (noting that "it was appropriate for the special master to consider the medical literature presented, including the IOM report" and that "the court often has relied on the findings of the Institute of Medicine."); *See also, Isaac v. Sec'y Health & Human Servs.,* 108 Fed. Cl. 743, 755 (2013), *aff'd,* 540 Fed. Appx. 999 (Mem.) (Fed. Cir. 2013) (affirming the special master's reliance on findings of the IOM); *Porter v. Sec'y Health & Human Servs.,* 663 F.3d 1242, 1252 (Fed.Cir.2011) (noting the special master's comment that "IOM reports are favored, although not dispositive, in the Vaccine Act Program," then affirming the special master's decision); *Cedillo v. Sec'y Health & Human Servs.,* No. 98–916V, 2010 WL 331968, at *94 (Fed. Cl. Spec .Mstr. Feb. 12, 2009), *mot. for rev. denied,* 89 Fed. Cl. 158 (2009) (affirming special master's reliance on conclusions of IOM), *aff'd,* 617 F.3d 1328 (Fed.Cir.2010); *Rodriguez v. Sec'y Health & Human Servs.,* 67 Fed. Cl. 409, 410 (2005) (relying on IOM report regarding vaccine causation of an injury); *Althen v. Sec'y Health & Human Servs.,* No. 00–170V, 2003 WL 21439669, at *11, n.28 (Fed. Cl. Spec. Mstr. June 3, 2003) ("Due to the IOM's statutory charge, the scope of its review, and the cross-section of experts making up the committee reviewing the adverse events associated with vaccines, the court considers their determinations authoritative and subject to great deference."), *rev'd on other grounds,* 58 Fed. Cl. 270, 272–74 (2003) (citing IOM reports frequently in support of various scientific propositions), *aff'd,* 418 F.3d 1274 (Fed. Cir. 2005); *Terran v. Sec'y Health & Human Servs.,* 41 Fed. Cl. 330, 337 (1998) (affirming special master's reliance on conclusions of IOM), *aff'd,* 195 F.3d 1302 (Fed. Cir.1999), *cert. denied,* 531 U.S. 812 (2000); *Cucuras v. Sec'y Health & Human Servs.,* 993 F.2d 1525, 1529 (Fed. Cir. 1993) (noting that the special master had placed "a great deal of weight" on an IOM report in reaching a decision, then affirming the special master's decision); *Stroud v. Sec'y Health & Human Servs.,* 113 F.3d 1258 (Fed. Cir. 1997) (unpublished)(special master may rely upon an IOM report that neither party filed as evidence); *Ultimo v. Sec'y Health & Human Servs.,* 28 Fed. Cl. 148, 152 (1993) (proper for a special master to rely on IOM report).

[31] It should be noted that the IOM committee's apparent decision to selectively cite from the relevant body literature for its report does not *a fortiori* demonstrate bias against the finding of a causal relationship. For example, the committee did not cite the Guggenheim article discussed below, which pre-dates the 2012 IOM report and casts further doubt on the Goodman findings that were discussed by the committee. Especially given that the IOM committee did review the primary piece of evidence cited by Dr. Kinsbourne – that is, the NCES data albeit as examined by Goodman rather than Bellman – Dr. Kinsbourne's critique would be much stronger if he were able to identify potentially persuasive evidence of a causal relationship that represented a significant omission. The IOM committee's conclusion that there is not sufficient evidence to accept or reject a causal relationship is not inconsistent with the Goodman study's overall conclusion despite its additional finding as to a temporal shift.

subclinical to a clinical disorder." (Tr. 139.) However, to the extent Bellman includes a specific finding that provides some limited support for the notion of a vaccine-triggered infantile spasms, passage of time has not borne out that hypothesis any further and, in fact, subsequent studies have called the very premise into question.

Specifically, Dr. Holmes has filed studies from 2008 by Philippi et al., and Guggenheim et al., which showed that infantile spasms actually develop over the course of weeks to months. Philippi, et al, retrospectively examined 39 infants with symptomatic infantile spasms. (Philippi et al., *Electroencephalographic evolution of hypsarrhythmia: Toward an early treatment option* 49(11) EPILEPSIA 1859-1864, 1859 (2008) (Ex. A, Tab 29.)) After examining the serial EEGs available for these subjects, they concluded that the evolution of the hypsarrhythmia underlying infantile spasms occurs in three phases, each of which lasts several weeks. (*Id*. at 5.) They found that mental deterioration due to infantile spasms begins 3-6 weeks prior to the onset of hypsarrhythmia. (*Id*. at 6.) Guggenheim et al., examined 19 published cases of infantile spasms. They examined the length of time between an encephalopathic event experienced by a previously normal infant and the onset of infantile spasms. (Guggenheim et al., *Time Interval From a Brain Insult to the Onset of Infantile Spasms,* J. PEDIAT. NEUROL. 34-37, 34 (2007) (Ex. A, Tab 25.)) They found that the latency between brain insult and onset of spasms ranged from six weeks to 11 months. (*Id*.) Thus, they concluded:

> [T]he results of our analysis preclude claims that the onset of infantile spasms within hours or days of immunization indicates a causal relationship, because such claims are based on the assumption that the brain is injured by a toxin present in the product, or by some unspecified aberrant immunologic process. Consequently, the observation that infantile spasms occur with an average latency of 5.1 months after postnatal injury is supportive of the already existing strong evidence that vaccine administration is not a causative factor in this disorder, and reinforces the generally held view that a close temporal association in occasional cases is only coincidental.

(*Id*. at 3.). These findings also support Dr. Holmes's emphasis throughout the hearing that infantile spasms are not "provoked" seizures. (Tr. 294-95, 320-21, 323, 354.)

Even setting aside these subsequent studies, an additional issue with Dr. Kinsbourne's reliance on the Melchior and Bellman studies is the transition away from the whole cell pertussis vaccines ("DPT") studied by Melchior and Bellman toward acellular formulations of pertussis-containing vaccines ("DTaP") that are generally considered to be much safer. This transition dates these studies and leaves them further attenuated from current realities. Thus, for example, the 2011 von Spiczak paper relied on by petitioner observes that there is no elevated risk of epilepsy following DTaP vaccination. (von Spiczak, *supra,* at Ex. 36, p. 2.) Petitioner also cites a 2002

package insert for the DAPTACEL DTaP vaccine.[32] (DAPTACEL package insert, Ex. 55.) That insert identifies seizures occurring within three days of vaccination (with or without fever) as adverse reactions but does not include infantile spasms as adverse reactions among its Warnings and Precautions. (*Id*. at 4-5.) DAPTACEL discloses nine clinical trials with 18,000 doses administered with only a single report of infantile spasms reported.[33] (*Id*. at 6-14.)

Especially because Melchior and Bellman at best demonstrate statistical observations and not mechanistic evidence, what is purportedly demonstrated with respect to the DPT vaccine does not automatically translate to the DTaP vaccine. This was a point stressed by Dr. Holmes during the hearing. (Tr. 309-10.) Dr. Kinsbourne attempts to overcome this issue by suggesting that both DPT and DTaP vaccinations promote similar proinflammatory cytokine output and further stressing that "I've never seen any article that said they eliminated the reaction."[34] (Ex. 24, p.3; Tr. 144.) However, Dr. Kinsbourne is unpersuasive on this point for several reasons.

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[32] There is no evidence of record indicating what specific brand of vaccination D.B. received.

[33] Petitioner highlights the fact that the contraindications include progressive neurological disorders including infantile spasms and notes that the "Pertussis vaccine should not be administered to individuals with such conditions until a treatment regimen has been established and the condition has stabilized." (DAPTACEL package insert , *supra,* at Ex. 55, p. 4.) According to Dr. Kinsborne, this is an acknowledgement that the pertussis vaccine is more likely than other vaccines to cause seizures when there is already brain inflammation present. (Tr. 145.) Dr. Holmes disagreed and stressed during the hearing that this is not an indication that the vaccine causes infantile spasms. (Tr. 311-12.) For a more detailed discussion of the information contained in package inserts, *see Cottingham v. Sec'y of Health & Human Servs.*, 15-1291V, 2021 WL 347020, *23-26 (Fed. Cl. Spec. Mstr. Jan. 7, 2021), *vacated on other grounds*, 154 Fed. Cl. 790 (2021). In some prior cases, special masters have concluded broadly that "[s]tatements contained in vaccine package inserts do not constitute reliable proof of causation, and cannot be deemed admissions that the vaccines in question have the capacity to harm a particular petitioner in a specific manner." *Sullivan v. Sec'y of Health & Human Servs.,* No. 10-398V, 2015 WL 1404957, at *20 (Fed. Cl. Feb. 13, 2015) (citing *Werderitsh v. Sec'y of Health & Human Servs.,* No. 99–319V, 2005 WL 3320041, at *8 (Fed. Cl. Spec. Mstr. Nov. 10, 2005); *see also* 21 C.F.R. § 600.80(l). The *Cottingham* special master, however, further distinguished as more valuable information provided by the clinical trials described by the package insert. 2021 WL 347020, *23-26. Here, as noted above, the clinical trials do not appear to support infantile spasms as an adverse reaction to DAPTACEL, which is consistent with the fact that only seizures, and not infantile spasms or epilepsies, are included among the Warnings and Precautions despite the language of the contraindication. (DAPTACEL package insert, *supra,* at Ex. 55, p. 4-5.) Additionally, while post marketing experience includes febrile convulsions, grand mal convulsions, and partial seizures, infantile spasms were not reported. (*Id*. at 16.) The specific basis for including uncontrolled epilepsies among the contraindications is not indicated (*i.e.* there is no citation to either the clinical data or any other literature).

[34] Of note, in *Kottenstette* the Federal Circuit has addressed a similar scenario wherein Dr. Kinsbourne opined before a different special master that the Bellman and Melchior studies could be relied upon in the context of the DTaP vaccine based on the notion that DTaP only imperfectly improved the safety of pertussis immunizations. 861 Fed.Appx at 441-42. The Federal Circuit concluded that the special master did not abuse her discretion by crediting Dr. Kinsbourne's testimony as supporting reliance on the Bellman and Melchior studies. *Id*. However, nothing in the Federal Circuit's holding mandates the outcome reached in that case. Moreover, the Federal Circuit stressed that the special master in *Kottenstette* did not reach her conclusion based solely on the Bellman and Melchior studies. *Id*. at 441. In that case, Dr. Kinsbourne relied on a different rationale. Whereas here he opines that the adverse effect profile carries over based on the cytokines produced by the two vaccines, in *Kottenstette* he opined

First, he seeks to extend the Bellman and Melchior findings by relying in large part on unrelated findings relating to unitary post-vaccination seizure events rather than the infantile spasms examined by Bellman and Melchior. For example, in addition to the package insert discussed above, he relies on a 2003 Canadian study be Le Saux et al., which examined post-vaccination febrile and afebrile seizures, but does not include information regarding any form of epilepsy let alone infantile spasms specifically. (Tr. 141-42, 245; Le Saux et al., *Decrease in Hospital Admissions for Febrile Seizures and Reports of Hypotonic-Hyporesponsive Episodes Presenting to Hospital Emergency Departments Since Switching to Acellular Pertussis Vaccine in Canada: A Report from IMPACT,* 112 PEDIATRICS 1-8 (2003) (Ex. 83.)) The idea that DTaP can cause isolated seizures, especially febrile seizures, is not disputed in this case (Tr. 323-24, 344-45 (Holmes)) whereas even the more up to date literature filed by Dr. Kinsbourne (von Spiczak) acknowledges the suggestion of a relationship between infantile spasms and vaccinations to be controversial. (Ex. 36, p. 10)[35] Dr. Holmes likewise testified that unitary seizures and infantile spasms cannot be conflated. (Tr. 309-10.)

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that the toxoiding process that creates the acellular pertussis component of the vaccine is imperfect and adverse events following DTaP can be attributed to direct effects of residual untoxoided pertussis toxin within the vaccine. *Kottenstette*, 861 Fed.Appx. 436-37. In decisions dating back years, other special masters have been critical of attempts to carry over statistical observations from one vaccine formulation to the other. *See, e.g.*, *Taylor v. Sec'y of Health & Human Servs.*, No. 05-1133V, 2012 WL 4829293, at *30 (Fed. Cl. Spec. Mstr. Sept. 20, 2012) ("[i]t is well established that, while pertussis toxin may be capable of causing neurological damage, vaccination, especially modern-day vaccination with *the acellular form*, is generally safe") (emphasis added); *Holmes v. Sec'y of Health & Human Servs.*, No. 08-185V, 2011 WL 2600612, at *20 (Fed. Cl. Spec. Mstr. Apr. 26, 2011) (noting that expert in question had previously attempted to extrapolate conclusions from studies involving DPT to DTaP vaccines), citing *Simon v. Sec'y of Health & Human Servs.*, No. 05-941V, 2007 WL 1772062, at *7 (Fed. Cl. Spec. Mstr. June 1, 2007) ("the relative risks of an adverse event from a DPT vaccine found in those DPT related epidemiologic studies do not attach to a DTaP vaccine"); *Grace v. Sec'y of Health & Human Servs.*, No. 04-[redacted], 2006 WL 3499511, at *9 (Fed. Cl. Spec. Mstr. Nov. 30, 2006) (noting that "[t]he DTaP version, in general, is believed by medical scientists to be much improved, and to be much less likely than the DPT vaccine to cause neurologic reactions or other harmful side effects.") Moreover, Dr. Kinsbourne's framing of the issue as requiring affirmative proof of an "elimination" of the risk is not really consistent with how epidemiology functions or petitioner's burden of proof. The question posed from an epidemiologic standpoint would more likely be whether the incidences of infantile spasms following DTaP vaccination remain statistically observable as compared to the general population or to controls. Dr. Kinsbourne has not cited any evidence to suggest that they are. The von Spiczak paper from 2011 acknowledged the possibility, but explicitly indicated that they did not reach that question based on their own data and otherwise observed based on other studies that the risk of epilepsies following DTaP vaccine is not elevated. (von Spiczak, *supra,* at Ex. 36, p. 2.) The 2012 IOM report likewise indicated that insufficient evidence is available to accept or reject a causal relationship between infantile spasms and the DTaP vaccine. (IOM, *supra,* at Ex. A, Tab 14, p. 539.) In a cause-in-fact claim, it is petitioner's burden to affirmatively present a *prima facie* showing of vaccine causation. Petitioner cannot simply assert *ipse dixit* that a specific vaccine formulation is unsafe and call on the respondent to prove a negative.

[35] To be clear, Dr. Kinsbourne did also opine that D.B. suffered a tonic seizure that was triggered by his vaccination and then subsequently evolved into infantile spasms. (Tr. 135-37 (citing Carrazana et al., *supra,* at Ex. 92.)) That aspect of Dr. Kinsbourne's opinion is addressed separately below. Here I note only that comparison of the Bellman and Melchior studies to studies involving unitary seizures is not an "apples to apples" comparison that could support extension of the earlier studies' findings to other vaccine formulations.

Additionally, even if there can be some intersection between neurology and immunology, Dr. Kinsbourne is well outside his area of expertise in purporting to opine as to the relative reactogenicity of different vaccine formulations based on their immunogenicity. Nor is it clear from the face of the study he cites, which administered pertussis toxin, rather than vaccines, to mice, how the study's findings correlate to the human response to different vaccine formulations. (Chen et al., *Pertussis Toxin by Inducing IL-6 Promotes the Generation of IL-17-Producing CD4 cells,* 178(10) J. IMMUNOL. 1-13 (2007) (Ex. 30.)) By contrast, Dr. Holmes cites a study finding evidence of lower reactogenicity among infants receiving DTaP vaccine compared to DPT (Stehr et al.), as well as a competing mouse model study (Donnelly et al.), showing that the whole cell pertussis vaccine, but not the acellular pertussis vaccine, produced convulsive levels of proinflammatory cytokines. (Ex. A, p. 9 (citing Stehr, et. al, *A Comparative Efficacy Trial in Germany in Infants Who Received Either the Lederle/Takeda Acellular Pertussis Component DTP (DTaP) Vaccine, the Lederle Whole-Cell Component DTP Vaccine, or DT Vaccine,* 101(1) PEDIATRICS 1-13, 9 (1998) (Ex. A, Tab 21); Ex. A, p. 11-12 (citing Donnelly et al., *Whole-Cell but Not Acellular Pertussis Vaccines Induce Convulsive Activity in Mice: Evidence of a Role for Toxin-Induced Interleukin-1β in a New Murine Model for Analysis of Neuronal Side Effects of Vaccination,* 69(7) INFECT. IMMUN. 4217-4223 (2001) (Ex. A, Tab 23.))

The record is not entirely without evidence consistent with Dr. Kinsbourne's view – most notably the temporal shift observed by Bellman.[36] On the whole, however, Dr. Holmes was more persuasive in testifying that, although the initial investigation into whether whole cell pertussis can be causally linked to infantile spasms may have been justified, vaccinations are no longer viewed as a risk factor for the development of infantile spasms. (Tr. 304-05.) As a general matter, it is true that petitioners in the Vaccine Program are not required to present epidemiological evidence to establish their causation burden under *Althen. Moberly v. Sec'y of Health & Hum. Servs.*, 592 F.3d 1315, 1325 (Fed. Cir. 2010). Nonetheless, "[n]othing in *Althen* or *Capizzano* requires the Special Master to ignore probative epidemiological evidence that undermines petitioner's theory." *D'Tiole v. Sec'y of Health & Human Servs.*, 726 F.App'x 809, 811 (Fed. Cir.) (citing *Andreu*, 569 F.3d at 1379 ("Although *Althen* and *Capizzano* make clear that a claimant need not produce medical literature or epidemiological evidence to establish causation under the Vaccine Act, *where such evidence is submitted*, the Special Master can consider it in reaching an informed judgment as to whether a particular vaccination likely caused a particular injury.") (emphasis added))); *Grant*, 956 F.2d at 1148-49 (considering negative epidemiological studies). Here, given that Dr. Kinsbourne also proposes a mechanism of injury, the lack of recognition of vaccinations as risk factors for infantile spasms is not necessarily dispositive, though Dr. Kinsbourne's mechanistic theory does in turn rely partly on the above-discussed literature. (Tr. 209.) At a minimum, however, it does provide important context in evaluating Dr. Kinsbourne's proposed mechanism, discussed below.

[36] In *Kottestette*, I previously characterized the temporal shift observed by Bellman as providing only "scant" evidence. 2020 WL 4197301, at *14. However, the Philippi and Guggenheim studies discussed above were not a part of the record of that case.

ii. Dr. Kinsbourne's proposed mechanism is not supported by preponderant evidence

Dr. Kinsbourne also purports to demonstrate a mechanism of injury. Specifically, he proposes that the immune and stress responses to a vaccine injection may act on the endocrine system to elevate corticotropin-releasing hormone ("CRH") and provoke infantile spasms. (Ex. 40, pp. 3-4; Tr. 152.) Alternatively, he suggests that vaccines may cause partial seizures and that partial seizures may then evolve into infantile spasms. (Tr. 135-37.) Dr. Kinsbourne cites several points that he urges as support for this theory:

- The human brain depends on a balance between inhibition and excitation of neuronal activity. The immature brain is more excitable than the adult brain. (Tr. 145-47 (*see also* Baram & Hatalski, *supra,* at Ex. 26, p. 1).) GABA is the principle inhibitory neurotransmitter in the mature central nervous system. (*Id.*)

- Down syndrome constitutes a predisposition to react adversely to excitatory influences. (Baram & Hatalski, *supra,* at Ex. 26, p. 3.)

- Cortez et al., demonstrated that infantile spasms can be caused in a mouse model of Down syndrome using an injection of Baclofen. (Tr. 145-47 (discussing Cortez et al., *Infantile Spasms and Down Syndrome: A New Animal Model,* 65 PEDIATRIC RESEARCH 499-503 (2009) (Ex. 85.)) Because Baclofen enhances GABA function, Dr. Kinsbourne contends that this study shows that infantile spasms operate via a GABA-mediated mechanism. This result is counterintuitive because enhancing GABA, which is inhibitory, would not be expected to cause seizures, which are excitatory.

- However, according to Dr. Kinsbourne a further study by Cullinen et al., further demonstrates that the body's stress response indirectly inhibits GABA, raising overall excitation in the brain. (Tr. 149-51 (discussing Cullinan et al., *Functional role of local GABAergic influences on the HPA axis,* BRAIN STRUCT. FUNCT. (2008) (Ex. 87.))

- Epilepsies are inflammatory states and vaccines release cytokines via the innate immune system. (Tr. 211.)

- Jansen et al., demonstrated that a heel stick causes a steroid reaction that affects the hypothalamic-pituitary-adrenal axis, i.e., the HPA axis. (Tr. 152-53 (discussing Jansen et al., *supra,* at Ex. 86).)

- Baram and Hatalski developed a theory of infantile spasms that posits the neurohormone corticotropin-releasing hormone ("CRH") modulates excitability in the developing brain and may account for the development

of seizures in response to stress or infection. (Baram & Hatalski, *supra,* at Ex. 26, p. 6.)

- Carrazana et al., reported 16 cases of infantile spasms beginning in close proximity to a partial seizure. (Tr. 135-36 (discussing Carrazana et al., *supra,* at Ex. 92.))

Pulling these points together, Dr. Kinsbourne opines that Down syndrome constitutes a preexisting susceptibility or "first hit" and that vaccines can act as a "second hit." The vaccine creates two stresses, the production of cytokines as part of the immune response and the pain of the needle. Acting upon the HPA axis via the stress response to over produce CRH, vaccination can induce a seizure, whether infantile spasms or a partial seizure. A partial seizure can then lead to infantile spasms. (Tr. 153, 214-15.) This theory has significant flaws at nearly every step.

First, Dr. Kinsbourne is not persuasive in contending that the two-hit hypothesis is an appropriate starting premise. Dr. Holmes distinguishes between Down syndrome as including a lowered threshold for seizure and as constituting a "first hit" in the two-hit hypothesis. (Tr. 298-300.) According to Dr. Holmes, the two-hit hypothesis involves the cumulative effect of multiple brain injuries as contributing to status epilepticus. (*Id*. (discussing Hoffman et al., *Cognitive impairment following status epilepticus and recurrent seizures during early development: support for the "two-hit" hypothesis,* Epilepsy & Behavior 873-77 (2004) (Ex. G); Koh et al., *NBQX or Topiramate Treatment after Perinatal Hypoxia-induced Seizures Prevents Later Increases in Seizure-induced Neuronal Injury,* 45(6) EPILEPSIA 569-575 (2004) (Ex. K)).) This is also consistent with the way in which Arya et al., filed by petitioner, categorize infantile spams in the context of Down syndrome as potentially being either cryptogenic or symptomatic depending on the presence of other factors. (Arya et al., *supra,* at Ex. 25, p. 2.) Moreover, Dr. Holmes explained that Guggenheim et al., demonstrates that even when there is an identified first hit, such as hypoxia, onset of infantile spasms occurs months later and without the necessity of a "second hit." (Tr. 301-02 (discussing Guggenheim et al., *supra,* at Ex. A, Tab 25).) In fact, Dr. Kinsbourne himself acknowledges that a second hit is not necessary to the manifestation of infantile spasms. (Tr. 208-09.)

Second, Dr. Holmes takes issue with Dr. Kinsbourne's reliance on the mouse studies by Cortez and Cullinen as well as upon the Baram hypothesis. (Tr. 315-17.) With respect to all three, Dr. Holmes stressed that none of these studies relate their findings to the context of vaccination. (*Id*.) Indeed, Baram only hypothesized that triggers such as fever, hypoxia, or trauma might contribute to seizures. (Ex.41, pp. 1-2.) With respect to the Cortez study, Dr. Holmes further stressed the point, also acknowledged by Dr. Kinsbourne, that the animal model did not have spontaneous spasms. (Tr. 315.) That is, Dr. Kinsbourne acknowledged that model of Down syndrome did not demonstrate infantile spasms except through the manufactured means of injecting Baclofen. Thus, Dr. Kinsbourne indicated that the model is "incomplete," and accepted that this was an "important point." (Tr. 146.)

Dr. Holmes also explained that the Baram hypothesis comes from a long-standing research interest of Dr. Tallie Baram in exploring whether the HPA axis could contribute to the triggering of infantile spasms. It was based on two observations. On the one hand, studies of the spinal fluid of children with infantile spasms found decreased levels of ACTh. (Tr. 317.) The fact that ACTh is an effective treatment for infantile spasms is well established. (Tr. 293-94.) On the other hand, an animal model study showed that injecting CRH into the brains of young animals can cause seizures (not infantile spasms). (Tr. 318.) According to Dr. Holmes, where the Baram hypothesis failed was in trying to bridge the two observations by using ACTh to prevent the CRH-induced seizures in the animal model. ACTh did not prevent the CRH-induced seizures. Thus, while the theory once merited attention, he indicates that it has since been abandoned.[37] (*Id.*)

In any event, assuming *arguendo* that infantile spasms are provoked by stress hormones, Dr. Kinsbourne has also not supported the idea that any of this would be triggered by vaccination. With respect to the stress response from a heel stick, he acknowledges that the Jensen article is inadequate to provide any suggestion that its findings of increased cortisol, which Dr. Holmes characterizes as mild, are clinically significant. (Tr. 246, 316.) Dr. Kinsbourne also acknowledges that the only basis for contending that infantile spasms are an inflammatory condition is his own assertion that they have a pro-inflammatory trigger. In the absence of such a trigger, he would not know if the condition was inflammatory. (Tr. 211-12, 213.) Confusingly, despite positing that the pertussis in the vaccine can cause seizures via pro-inflammatory cytokines, he also suggested that the Cortez mouse model suggests that you don't need a cytokine response to produce the elevated cortisol underlying the Baram hypothesis. (Tr. 218, 221.) He does not know of any animal model study that shows activation of the immune system causes infantile spasms and does not recall filing any literature identifying proinflammatory cytokines as a mechanism for post-vaccination infantile spasms. (Tr. 211-12, 213.) When asked during the hearing if any literature posits vaccination as a second hit within the two-hit hypothesis, he referred to the literature filed in this case demonstrating higher than expected incidences of infantile spasms following vaccination. (Tr. 209.) However, for all the reasons discussed above, that literature is not persuasive.

Finally, the ultimate lynch pin in Dr. Kinsbourne's alternative theory for this case is his reliance on the Carrazana article as demonstrating that a partial seizure can introduce infantile spasms. This is the sole support on this record for Dr. Kinsbourne's assertion that partial seizures can develop into infantile spasms. In fact, Dr. Kinsbourne testified that he cannot explain how a seizure can evolve into infantile spasms but for his reliance on the Carrazana article.[38] (Tr. 221.) However, Dr. Holmes's explanation

[37] In *Kottenstette*, I previously accepted Dr. Kinsbourne's reliance on the Baram hypothesis to the extent that it showed seizures can be triggered by stress. 2020 WL 4197301, at *14. In that case, there was no expert testimony challenging the Baram hypothesis's general acceptance.

[38] There is a theory known as the "kindling theory" in which initial seizures are suspected to bring about further seizures. Dr. Holmes explained, however, that the seizures involved in infantile spasms are not consistent with the kindling theory. (Tr. 350-52 (discussing Ben-Ari & Holmes, *Relevance of Basic*

of the Carrazana article (he is among the authors) persuasively established that Dr. Kinsbourne is misinterpreting that paper. (Tr. 286-90.)

Carrazana et al., is a report of 16 cases of infantile spasms in which the infantile spasms were preceded by or concurrent with partial seizures. (Carrazana et al., *supra,* at Ex. 92.) The authors suspected that the temporal proximity of the partial seizures to the infantile spasms may be causally relevant. Specifically, Dr. Kinsbourne highlights the following explanation: "'[t]his group of patients supports a model in which the spasms, though probably generated at a subcortical level, are facilitated or possibly induced [by] focal discharges from cortical pathology.'" (Tr. 136 (quoting Carrazana et al., *supra,* at Ex. 92, p. 1.) He opined that this article provides evidence that "[t]he vaccines surely triggered the partial seizures, not the infantile spasms. The partial seizures then transformed into infantile spasms." (Tr. 136.)

Dr. Holmes explains, however, that all of the sixteen subjects had focal abnormalities or lesions. This was a prerequisite to being included in the study. (Tr. 288-90.) Dr. Kinsbourne had not understood this as he denied that all of the Carrazana subjects had focal abnormalities. (Tr. 222.) This is significant because Carrazana did not identify partial seizures as causes of infantile spasms, but rather questioned in the specific context of focal abnormalities whether the partial seizures, as manifestations of the focal abnormality, were evidence that the infantile spasms were etiologically related to the focal cortical lesion as opposed to the partial seizure. Dr. Holmes explained that while Carrazana demonstrated that infantile spasms and focal seizures can occur at the same age, the bilateral generalized infantile spasms and the focal seizure remain two separate neuropathologic processes. (Tr. 287-88.) Dr. Holmes specifically testified that "we clearly show that they're not having focal seizures that then propagate into infantile spasms" (Tr. 290) and that "[b]y no means did that paper show that focal seizures cause infantile spasms." (Tr. 288.) Thus, the article stresses that as of its 1993 publication, "the role of the coexisting cortical lesions, whether critical for development of the spasms or merely coincidental, remains unknown" and that the paper instead suggests "an important role for cortical structures in the generation of spasms." (Carrazana et al., *supra,* at Ex. 92, p. 1.) Among these subjects, ACTh treatment was largely not effective and many were considered surgical candidates, points which distinguish these subjects from other patients with infantile spasms, including D.B. (Tr. 286-88; Carrazana et al., *supra,* at Ex. 92, p. 11.) That is, the Carrazana paper proposes an etiologic model for a specific subset of symptomatic infantile spasms involving cortical pathology not relevant to D.B.'s own history rather than any kind of causal relationship between partial seizures and infantile spasms. (Carrazana et al., *supra,* at Ex. 92, p. 1.)

For all these reasons, even if setting aside the discussion of epidemiology in the preceding section, Dr. Kinsbourne has not persuasively theorized that vaccines can in themselves cause infantile spasms. Nor has he persuasively theorized that an initial vaccine-caused partial seizure can cause or contribute to the onset of infantile spasms.

Research to Clinical Data: Good Answers, Wrong Questions!, 8(1) EPILEPSY CURRENTS, 19-22 (2008) (Ex. E.)) In any event, Dr. Kinsbourne never specifically cited this theory.

b. *Althen* Prong Two

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375–77; *Capizzano*, 440 F.3d at 1326; *Grant*, 956 F.2d at 1148. In establishing that a vaccine "did cause" injury, the opinions and views of the injured party's treating physicians are entitled to some weight. *Andreu*, 569 F.3d at 1367; *Capizzano*, 440 F.3d at 1326 ("medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury'") (quoting *Althen*, 418 F.3d at 1280). However, medical records and/or statements of a treating physician's views do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. *See* Section 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 746 n.67 (2009) ("there is nothing ... that mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted").

In this case, there is testimony indicating that D.B. had a fever during the evening following his February 14, 2015 vaccinations. (Tr. 67, 69.) Additionally, there is evidence that the DTaP vaccine can cause febrile seizures (Tr. 118 (Kinsbourne); 344-45 (Holmes)), though Dr. Kinsbourne is not specifically relying on the presence of a febrile seizure. (Tr. 222, 245-46). However, even if D.B. had initially experienced a post-vaccination seizure separate from his infantile spasms, Dr. Kinsbourne has not articulated how that one seizure could have developed into infantile spasms. As noted above, Dr. Kinsbourne testified that he cannot explain how a seizure can evolve into infantile spasms but for his reliance on the Carrazana article. (Tr. 221; Carrazana et al., *supra,* at Ex. 92.) Dr. Holmes was persuasive, however, in explaining that Dr. Kinsbourne misinterpreted the Carrazana paper. (Tr. 222, 286-90.) Dr. Kinsbourne's reliance on the Carrazana paper is further attenuated in that Dr. Holmes suggests Dr. Kinbourne is wrong to equate the tonic seizure he purports to identify in D.B.'s case with a partial seizure as discussed in Carrazana. (Tr. 320.) Although Dr. Kinsbourne opines that a focal injury is not necessary for a tonic seizure to occur, Carrazana involved partial seizures manifesting from focal pathology and Dr. Kinsbourne acknowledges D.B. had no focal injury.[39] (Tr. 221.) Dr. Kinsbourne also acknowledged that what he proposes would constitute an unusual presentation. (Tr. 246.)

In any event, Dr. Kinsbourne is also not persuasive in opining that D.B. actually experienced an initial partial or tonic seizure prior to onset of his infantile spasms. First, none of D.B.'s treating physicians diagnosed him with any type of seizure other than infantile spasms. In fact, D.B.'s treating neurologist (Dr. Armstrong-Wells) reviewed

[39] Dr. Kinsbourne nonetheless opined that inflammatory cytokines could have acted focally to cause a tonic seizure (Tr. 221); however, the basis for this statement is not clear.

video footage of D.B.'s early seizures and concluded that they are "classic for infantile spasms." (Ex. 2, p. 16.) Moreover, no objective evidence supports Dr. Kinsbourne's assertion. Dr. Kinsbourne acknowledges there is no medical record evidence to suggest that D.B. suffered focal seizures and that his opinion is based on descriptive evidence only. (Tr. 225, 244.) Yet, he did not personally observe the seizures and, again, his interpretation of these early seizures is directly contradicted by D.B.'s treating neurologist. (Ex. 2, p. 16.) Second, Dr. Kinsbourne's opinion is not consistent with the onset of D.B.'s own seizures. Specifically, while Dr. Kinsbourne suggested D.B.'s initial seizure was a tonic seizure because D.B. had body stiffness, D.B.'s parents were clear and consistent in indicating that his initial seizure activity was limited to staring episodes and that seizures inclusive of stiffness did not begin until the next day.[40] (*Compare* Tr. 220-21, 245 and Tr. 68, 72, 102-06.) Third, Dr. Holmes is persuasive in providing a competing expert opinion, consistent with that of the treating neurologist, that the description of onset provided by D.B.'s parents closely fits the pattern of onset of infantile spams rather than tonic seizures. (Tr. 318-22.) Dr. Holmes further explained that while the seizures seen in infantile spasms are a bit more prolonged than simple myoclonus, they are not tonic. (Tr. 270-71, 280.) The fact that the spasms occur in clusters is characteristic of the condition. (*Id*.)

Even setting aside the question of a partial or tonic seizure, the fact that D.B.'s infantile spasms arose post-vaccination does not in itself provide meaningful evidence supporting vaccine causation. Standing alone, a temporal association is not sufficient to satisfy *Althen* prong two. *Veryzer v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 344, 356 (2011) (explaining that a "temporal relationship alone will not demonstrate the requisite causal link and that petitioner must posit a medical theory causally connecting the vaccine and injury."). Moreover, Dr. Holmes has raised reasons to doubt there is any significance to the apparent temporality in this case. First, the condition of infantile spasms in itself has an age-related onset (first year of life) that matches the onset in D.B.'s case. (Ex. A, p. 9.) Relatedly, Dr. Kinsbourne acknowledges, consistent with Dr. Holmes's testimony that infantile spasms are not provoked seizures, that a specific trigger is not necessary for the onset of infantile spasms and that they can present

[40] Theoretically Dr. Kinsbourne could disagree that the initial staring episodes described by petitioner and Mr. Bangerter were actually seizures at all; however, this is not his opinion. Dr. Kinsbourne confirmed that his opinion is that the seizures began on the same day as the vaccinations. (Tr. 134, 153.) Notably, Dr. Kinsbourne based his opinion in part on a description of D.B.'s seizure activity contained in the medical records (Tr. 123-24; Ex. 1, p. 46); however, the record he relied upon is from February 17 and Dr. Kinsbourne agrees that by that time D.B.'s seizure activity represented infantile spasms. (Tr. 124.) The discrepancy between Dr. Kinsbourne's assumption and fact witness testimony regarding the nature of D.B.'s very first spasms on the evening of his vaccination also calls into question Dr. Kinsbourne's suggestion that onset of D.B.'s spasms was unusually abrupt. (Tr. 125-26.) In that regard, Dr. Holmes clarifies that any one individual seizure is necessarily abrupt by the nature of seizures. (Tr. 346-48.) Infantile spasms can be subtle enough to go unnoticed until they become more intense, but they can also be noticed abruptly. (Tr. 345.)

spontaneously. (Tr. 196-97, 220.) Second, D.B.'s Down syndrome represented a separate risk factor for the condition.[41] (Ex. A, p. 9.)

Given these factors, Dr. Kinsbourne is unpersuasive in dismissing the alternative to vaccine-causation as an unbelievable "cosmic coincidence."[42] (Tr. 227-28.) Without any basis to connect the two events (vaccination and injury onset), Dr. Kinsbourne's apparent reticence in applying the term coincidence does not serve to fill that gap or constitute actual evidence of causation. Dr. Kinsbourne is correct that coincidence would not necessarily be a satisfying explanation in the context of a truly mysterious injury with no other available explanation, but that is not the case here. That a child predisposed to suffering infantile spasms, a condition that does not require a trigger to manifest and has a known age-related period of onset, suffered that condition at the age when that condition typically manifests in no way requires invocation of coincidence to constitute a reasonable explanation for the occurrence of that injury.

Additionally, as discussed further with respect to *Althen* prong three, Dr. Holmes is persuasive in demonstrating that clinically overt infantile spasms have a weeks-to-months long latency period from initial insult, meaning that the cause-and-effect relationship suggested by Dr. Kinsbourne in this specific case is implausible. While the outward presentation of infantile spasms may appear sudden, Dr. Holmes explained that:

> [a] process this complex, this diffuse, this dramatic on EEG, just doesn't occur suddenly. Much different than someone that comes in who has status epilepticus, who suddenly goes into a prolonged seizure. The brain is – the arch of the EEG is remarkably dramatically abnormal from the very onset. Infantile spasms is a beast of a different nature in that it does evolve slowly . . . So the clinical aspect, at some point they have someone who notices something . . . But infantile – the hypsarrhythmia didn't start then, the process evolved.

(Tr. 347-48.)

Finally, petitioner also contends that one of D.B.'s treating neurologists (Dr. Chapman) "clearly linked the pertussis component of the DtaP vaccine to the seizures when he advised that D.B. should not get another pertussis containing vaccine in the future. The neurologist certainly accepted a cause and effect association between the

[41] Specifically, the prevalence of seizures among Down syndrome individuals is 1-13% compared to 1.5-5% in the general population and infantile spasms are the most common type of seizure activity among those with Down syndrome. (Ex. A, p. 9.)

[42] Dr. Kinsbourne relies in part on the logic that the closer in time two events are, the more difficult it is to attribute coincidence. (Tr. 227-28.) However, this is unpersuasive. Coincidences by definition have the appearance of concurrence without necessarily suggesting a causal relationship. What Dr. Kinsbourne is actually describing is a continuum between what can be viewed as coincidental and what is not even perceived as potentially connected.

pertussis vaccine that D.B. received and his seizures." (ECF No. 108, p. 9.) Specifically, a note within D.B.'s primary care records reports that Dr. Leland "spoke with Dr. Kevin Chapman at Children's Neurology and he recommended the [patient] not get the DTAP vaccine given his history, but rather the DT pediatric dose vaccine." (Ex. 1, p. 97.)

While petitioner is not unreasonable in interpreting this notation as showing Dr. Chapman to be open to an association between pertussis vaccination and seizures, a precaution against future vaccination is not actually an opinion that D.B.'s prior condition of infantile spasms was vaccine-caused. For example, the DAPTACEL package insert filed by petitioner indicates that the DTaP vaccine is contraindicated in the context of neurologic conditions such as infantile spasms without respect to the underlying cause of the condition and without including infantile spasms among the known adverse reactions to the vaccine.[43] (DAPTACEL package insert*, supra,* at Ex. 55, pp. 4-5.) In contrast to Dr. Chapman's precaution, D.B.'s neurology records do not record any view by his neurology team that his infantile spasms were caused by any of his vaccinations. Dr. Chapman's precaution is not wholly without evidentiary value and I have considered it; however, especially in light of petitioner's failure to meet her burden under *Althen* prongs one and three, it is not enough without more to carry petitioner's burden under *Althen* prong two.

c. *Althen* Prong Three

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id.* at 1352; *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 503 Fed.Appx. 952 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Human Servs.*, No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

Petitioner's failure to establish *Althen* prong one in this case necessarily means she cannot establish *Althen* prong three. Dr. Holmes has persuasively explained that due to the way in which infantile spasms develop, the initial onset of D.B.'s first spams

[43] It is also worth noting that Dr. Chapman's recommendation actually exceeds the contraindication included in the DAPTACEL package insert in that the package insert indicates only that the vaccine is contraindicated for neurologic conditions that are untreated or not yet stabilized. (DAPTACEL package insert, *supra,* at Ex. 55, p. 4.) By the time Dr. Chapman was consulted for this precaution, D.B.'s infantile spasms had completely resolved. For his part, Dr. Holmes indicates that he recommends that all of his patients get all immunizations on schedule, including DTaP. (Tr. 323.)

could not be temporally related to a trigger occurring just hours earlier. The studies by Philippi et al., and Guggenheim et al., show that infantile spasms actually develop over the course of weeks to months. (Guggenheim et al., *supra,* at Ex. A, Tab 25; Philippi et al., *supra,* at Ex. A, Tab 29.)) Guggenheim et al., further demonstrated that the latency between an encephalopathic event and onset of infantile spasms was between six weeks to 11 months. (Guggenheim et al., *supra,* at Ex. A, Tab 25, p. 34.) The Guggenheim study explicitly refutes the temporal shift observed by Bellman within the first week following vaccination. (*Id*.) In the interest of completeness, I do note that Dr. Kinsbourne is persuasive in establishing that it is medically reasonable to attribute a seizure occurring within three days of a DTaP vaccination to that vaccine. (*See, e.g.,* DAPTACEL package insert, *supra,* at Ex. 55; Le Saux et al., *supra*, at Ex. 83.) However, as discussed above, this is not consistent with what D.B. actually experienced. Asked if the hypsarrhythmia underlying infantile spasms can develop within one day, Dr. Kinsbourne indicated that he does not know. (Tr. 231.)

d. Weighing the Competing Expert Opinions

Where both parties offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d at 1362). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146, 118 S. Ct. 512, 139 L.Ed.2d 508 (1997)); *see also Isaac v. Sec'y of Health & Human Servs.*, No. 08–601V, 2012 WL 3609993, at *17 (Fed. Cl. Spec. Mstr. July 30, 2012), *mot. for review den'd*, 108 Fed. Cl. 743 (2013), *aff'd*, 540 Fed. Appx. 999 (Fed. Cir. 2013) (citing *Cedillo*, 617 F.3d at 1339). Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Moberly*, 592 F.3d at 1325–26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Human Servs.*, 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

In determining whether a particular expert's testimony was reliable or credible, a special master may consider whether the expert is offering an opinion that exceeds the expert's training or competence. *Walton v. Sec'y of Health & Human Servs.*, No. 04–503V, 2007 WL 1467307, at *17–18 (Fed. Cl. Spec. Mstr. Apr. 30, 2007) (otolaryngologist not well suited to testify about disciplines other than her own specialty). While all testimony of the experts offered at the entitlement hearing was heard and considered, a special master may properly evaluate, and give appropriate weight to, whether certain testimony is beyond a particular expert's purview. *See*, *e.g., King v. Sec'y of Health & Human Servs.*, No. 03-584V, 2010 WL 892296, at *78–79 (Fed. Cl. Spec. Mstr. Mar. 12, 2010) (petitioner's expert far less qualified to offer opinion

on general causation issues pertaining to autism than specific issues pertaining to the petitioner's actual medical history, given the nature of the expert's qualifications).

Here, Dr. Kinsbourne was accepted without objection as an expert in pediatric neurology. (Tr. 117.) However, respondent stresses in his briefing his view that Dr. Kinsbourne's opinion is of "minimal value" based on several factors. (ECF No. 90, pp. 11-14.) Respondent stresses that Dr. Kinsbourne's credentials do not include any education, training, or expertise in pediatric immunology or seizure disorders. (*Id*. at 11.) He also stresses that Dr. Kinsbourne's career has largely focused on neuropsychology. (*Id*. at 11-12.) Respondent also argues that Dr. Kinsbourne's retirement in the 1990's renders his clinical experience remote. (*Id*. at 12.) (Dr. Kinsbourne took a nonmedical position with the New School in the early 1990's which ended after 20 years or about four to five years prior to the hearing in this case (Tr. 116).) Respondent cites a number of cases in which special masters have weighed the specifics of Dr. Kinsbourne's background in the context of assessing his opinion with respect to pediatric epilepsy.[44] (ECF No. 109, pp. 12-13.)

I have previously been critical of Dr. Kinsbourne for opining beyond his area of expertise and into the field of immunology. *Kottenstette*., 2020 WL 4197301 at *13-14, *review denied, decision aff'd*, No. 15-1016V, 2020 WL 4592590 (Fed. Cl. July 27, 2020), *rev'd on other grounds*, 861 Fed. Appx. 433 (Fed. Cir. 2021). However, I have also declined to credit respondent's arguments regarding Dr. Kinsbourne's retirement in some circumstances based on the specific contours of his testimony. *Eilan v. Sec'y of Health & Human Servs.,* No. 15-381V, 2021 WL 1085925, at *29-31 (Fed. Cl. Spec. Mstr. Feb. 23, 2021). In this case Dr. Kinsbourne's reliance on seemingly outdated materials and his lack of any recent clinical experience relative to pediatric epilepsy does dovetail with respondent's criticism and does affect the weight of his testimony in this case. Dr. Kinsbourne did have some notable experience in the 1950's and 1960's at Great Ormond Hospital with respect to the early use of ACTh in the treatment of infantile spasms (Tr. 200-01); however, that experience was limited and was decades ago (Tr. 201-02). Dr. Kinsbourne acknowledged that it has been decades since he last administered ACTh therapy to any patient. (Tr. 240.) Moreover, although Dr. Kinsbourne's CV reflects that he has an extensive publication history, it is unrevealing of

[44] Specifically: *Martin v. Sec'y of Health & Human Servs.,* No. 15-789V, 2020 WL 4197748, at *7, 31 (Fed. Cl. Spec. Mstr. May 8, 2020), *aff'd*, *Martin v. Sec'y of Health & Human Servs.*, No. 15-789V, slip op (Fed. Cl. 2020) ("Dr. Kinsbourne . . . has no demonstrated research or treatment expertise in the matters in dispute, and he relies on neurology expertise that has not been honed or refined, whether by clinical practice or research, for nearly 30 years."); *Jaafar v. Sec'y of Health & Human Servs.*, No. 15-267V, 2018 WL 4519066, at *3 (Fed. Cl. Spec. Mstr. Aug. 10, 2018) (concluding that petitioner did not establish DTaP vaccination caused infantile spasms and noting that "the most recent phase of [Dr. Kinsbourne's] career has had a shallower connection to pediatric neurology clinical care."); *Holmes*, 2011 WL 2600612 at *20 (questioning Dr. Kinsbourne's "clinical expertise in diagnosing and treating febrile seizures and epilepsy"); *Stone v. Sec'y of Health & Human Servs.*, No. 04-1041V, 2010 WL 1848220, at *8 (Fed. Cl. Spec. Mstr. Apr. 15, 2010), *review granted, judgment rev'd sub nom*; *Stone v. Sec'y of Health & Human Servs.*, 95 Fed. Cl. 233 (2010) ("The fact that for the past twenty-five years Dr. Kinsbourne has not focused his practice, research or teachings in the field of seizure disorders, . . . significantly limited his ability to offer reliable, persuasive, and cogent testimony in this case."); *Hoskins v. Sec'y of Health & Human Servs.,* No. 15-071V, 2017 WL 3379270, at *5 (Fed. Cl. Spec. Mstr. July 12, 2017).

any significant body of publications directly relevant to the condition of infantile spasms. (Ex. 23, pp. 5-33.) It is also the case that key elements of Dr. Kinsbourne's mechanistic theory are grounded in immunology, a subject beyond his area of expertise. Although immunology and neurology can intersect in the etiology of pediatric neurologic conditions, Dr. Kinsbourne here is attempting to leverage immunologic concepts to circumstantially establish a role for vaccines in the onset of infantile spasms in the face of direct investigation of that possibility that has suggested the lack of such a role. Moreover, his premise for leveraging evidence relating to different vaccine formulations to the DTaP vaccine is to compare the relative reactogenicity of the different formulations.

Dr. Holmes was also accepted as an expert in pediatric neurology; however, petitioner did object to an additional designation of Dr. Holmes as having a specialty in seizure disorders. (Tr. 268-69.) According to petitioner, Dr. Holmes's practice "sounds like a very general pediatric neurology practice." (*Id.*) Petitioner stressed that all pediatric neurologists see patients with seizures along with other things and that given the broad description of his practice, he is not out of the ordinary for a pediatric neurologist. (*Id.*) Petitioner is correct that Dr. Holmes described a full neurology practice in which he devotes only a single day per week to epilepsies and sees only about five or six infantile spasms patients per year. (Tr. 263, 266.)

Petitioner's objection is unpersuasive, however, when viewing Dr. Holmes's background and credentials as a whole. In addition to his clinical practice, Dr. Holmes has a long career in research relating to childhood epilepsies. (Tr. 263-64.) Dr. Holmes has developed animal models and done *in vivo* and *in vitro* laboratory studies addressing the effects of seizures and epilepsies on brain development. (Tr. 264.) His curriculum vitae lists two ongoing research grants, both on the topic of seizures, as well as 313 peer-reviewed articles of which well over 100 directly reference seizures. (Ex. B, pp. 26, 33-59.) Dr. Holmes represents that he has developed an animal model of infantile spasms and has published 19 studies specifically on infantile spasms. (Tr. 265-66.)

Even setting aside the specific designation of a specialty in seizure disorders and treating both Dr. Kinsbourne and Dr. Holmes as pediatric neurologists generally, comparison of the two experts' curriculum vitae still shows that they are not on equal footing with respect to their background in seizure disorders. (*Compare* Ex. B and Ex. 23.) Dr. Holmes has more, and much more up-to-date, experience, both clinically and in research, regarding seizure disorders generally and infantile spasms in particular.

e. Pneumococcal and other vaccines

I note briefly that D.B. received a number of vaccines at his six-month check up on February 14, 2014. Of those vaccinations, his DTaP vaccine garnered by far the most attention in this case. Other than DTaP, only his pneumococcal vaccine was invoked during the hearing. Specifically, while Dr. Kinsbourne excluded most of D.B.'s other vaccinations, Dr. Kinsbourne did cite the pneumococcal vaccine in his causal

opinion. (Tr. 122-23, 203.) However, he acknowledged that the literature linking the pneumococcal vaccine to seizures is less robust than the evidence regarding the DTaP vaccine and that petitioner did not file any literature pertaining specifically to the pneumococcal vaccine. (Tr. 203.) Here, I note in the interest of completeness that, in light of the analysis above pertaining to the DTaP vaccine, there is likewise not preponderant evidence that any of D.B.'s other February 14, 2014 vaccinations, including his pneumococcal vaccine, causally contributed to his infantile spasms alone or in combination with his DTaP vaccine.

f. Six months of Sequela

Even if petitioners did succeed in demonstrating that D.B.'s infantile spasms were vaccine-related, a remaining question would be whether they also established that D.B. suffered complications or residual effects of his condition lasting at least six months. In order to state a claim for a vaccine-related injury under the Vaccine Act, a vaccinee must have either:

> (i) suffered the residual effects or complications of such illness, disability, injury, or condition for more than 6 months after the administration of the vaccine, or (ii) died from the administration of the vaccine, or (iii) suffered such illness, disability, injury or condition from the vaccine which resulted in inpatient hospitalization and surgical intervention.

§ 300aa-11(c)(1)(D).

In this case, however, following his successful treatment with ACTh, D.B. was seizure free as of March 3, 2014. (Ex. 2, p. 171; Tr. 132-33.) Moreover, an EEG of March 13, 2014, demonstrated resolution of D.B.'s hypsarrhythmia.[45] (Ex. 7, p. 166; Tr. 133-34.) This is less than six months following the vaccination(s) at issue. Moreover, neurological exams conducted on February 18 and February 26, 2014, as well as an MRI study performed on February 27, 2014, showed no evidence of neurological damage. (Ex. 7, pp. 13-16 (February 18 exam); Ex. 7, pp. 67-69 (February 26 exam); Ex. 2, pp. 77-78 (February 27 MRI); Tr. 131, 332-35). Around the time of his vaccination, D.B. did experience some loss of milestones, namely a loss of head control and some reduction of social response. (Tr. 162-63 (discussing Ex. 3, pp. 24-25); Ex. 2, pp. 61, 67.) However, D.B.'s medical records and the testimony of his occupational therapist confirm not only that he had regained these milestones within six months, but also that he had resumed making progress beyond his prior baseline. (Tr. 186 (discussing Ex. 3, p. 41); *see also* Tr. 237-38 (Dr. Kinsbourne agreeing); Ex. 7, p. 351 (Dr. Dingman noting return of milestones and additional developmental gains as of July 8, 2014).) None of this is necessarily surprising as both neurology experts opined that it is possible for infantile spasms to be transient and without lasting neurologic damage.

[45] While Dr. Kinsbourne identified some additional abnormality relative to the March 13, 2014 EEG, a later April 7, 2014 EEG was entirely normal. (Ex. 7, p. 166.)

Petitioner's neurology expert, Dr. Kinsbourne, explained that "infantile spams usually have an adverse impact on child development, which may be massive and permanent, but in favorable cases is minor and recoverable[;]" and the "severity of the impact on development is in part mediated by the duration of the spasms and is mitigated when the spasms are readily suppressed by treatment, notably ACTh." (Ex. 20, p. 2.) Dr. Kinsbourne further explained that infantile spasms occurring in children with Downs syndrome "are unusually responsive to treatment," including treatment with ACTh. (Ex. 20, p. 2 (citing Nabbout et al., *Infantile Spasms in Down Syndrome: Good Response to a Short Course of Vigabatrin,* 42(12) Epilepsia 1580-1583 (2001) (Ex. 21, p. 4)).) With regard to D.B.'s own recovery, Dr. Kinsbourne opined that D.B.'s response to ACTh treatment was "specifically wonderful" and the fact that his final spasm was on March 3 was "spectacular." (Tr. 131.)

Dr. Holmes further explained that in infantile spasms the outward seizure activity is merely the "tip of the iceberg." (Tr. 272.) "The seizures come and go . . . [but] the hypsarrhythmic EEG is there 24 hours a day, seven days a week." (*Id.*) The hypsarrhythmic activity is what accounts for regression. (*Id.*) For example, he explained that the presence of visual agnosia is an indicator that hypsarrhythmia is interfering with the processing of information in the brain. (Tr. 276-77, 330-31.) Where infantile spasms lead to permanent effects, it is because prolonged periods of hypsarrhythmia have prevented neuronal development and connectivity in different parts of the brain critical to the developmental stage. (Tr. 277-78.) Even where there is later some improvement, these deficits cannot be recouped because the critical developmental period is inherently lost. (*Id.*) However, when the hypsarrhythmia is resolved quickly, children do quite well. (Tr. 277.)

Consistent with Dr. Kinsbourne's testimony, Dr. Holmes also cited a study by Stafstrom, showing that children with Down syndrome who experience infantile spasms tend to have good outcomes vis-à-vis regression. (Stafstrom, *Epilepsy in Down Syndrom: Clinical Aspects and Possible Mechanisms,* 98 AM. J. ON MENTAL RETARDATION 12-26 (1993) (Ex. A, Tab 7.)) Additionally, that study suggested that the regression, if any, is limited to the period of the spasms and a little before. (*Id.*) An additional article by Kivity et al., indicates that early intervention improves outcomes. (Kivity et al., *Long-term Cognitive Outcomes of a Cohort of Children with Cryptogenic Infantile Spasms Treated with High-dose Adrenocorticotropic Hormone,* 45(3) EPILEPSIA 255-262 (2004) (Ex. J.)) According to Dr. Holmes, "infantile spasms are pretty serious and are associated with regression, but not all is lost if you treat these children, some of them will do quite well, including those with Down syndrome." (Tr. 292.) In his personal experience, infantile spasms patients with Down syndrome do very well, especially with ACTh therapy. (Tr. 293.)

For D.B., Dr. Holmes explained that his normal EEG within four weeks is "a winner" and indicative of a very good prognosis. (Tr. 281.) He also noted that, while D.B. did have a period of inattentiveness, he did not demonstrate the type of visual agnosia that would indicate hypsarrhythmic damage. (Tr. 331.) Dr. Holmes agreed that D.B. continues to face developmental challenges due to his Down syndrome, but these

are not due to his infantile spasms. (Tr. 342.) Dr. Holmes opined that D.B. is no worse off now than he would have been but for his infantile spasms. (*Id*.)

Additionally, petitioner testified that as of his first birthday, D.B. was "very similar" to what he had been like prior to his infantile spasms. (Tr. 91-92.) D.B. was born on July 22, 2013, and the vaccinations at issue were administered February 14, 2014. Accordingly, D.B.'s first birthday occurred less than six months after his alleged vaccine injury. Petitioner recalled that he was sitting up, reaching for objects, could hold his head up, and that his gross-motor coordination difficulties had resolved. (*Id*.) As of that point, petitioner's only concerns were that D.B. had difficulty grasping his spoon and difficulty swallowing (*Id*.), two concerns addressed separately below.

Petitioner raises several different arguments for why D.B. did experience further residual effects or complications beyond six months from vaccination. Petitioner contends that even in the absence of permanent neurologic damage, D.B.'s infantile spasms changed the trajectory of his development. (ECF No. 108, p. 2.) In effect, petitioner argues that even the temporary period during which D.B.'s development was stalled due to the infantile spasms carried an opportunity cost. Even if he returned to and exceeded his baseline within six months, he would necessarily have been still farther along in development but for the infantile spasms. (*Id*. at p. 6.) Additionally, petitioner identifies two specific problems – difficulty swallowing and a left-hand fine motor deficit – that have persisted indefinitely and which petitioner contends are direct sequela of the infantile spasms. (ECF No. 108, p. 4) Also, a known side effect of ACTh therapy is weight gain. Petitioner contends that D.B. gained significant weight due to his ACTh therapy and that his weight did not normalize until sometime after his first birthday and interfered with his development. (ECF No. 108, p. 1.) On the whole, petitioner is not persuasive in demonstrating that D.B. suffered complications or residual effects of his infantile spasms for greater than six months.

i. Developmental trajectory

Petitioner's argument with respect to D.B.'s developmental trajectory has an attractive logic. However, petitioner has not provided preponderant evidence substantiating that D.B.'s brief period of infantile spasms resulted in a change in his overall developmental trajectory beyond six months post-vaccination. Although there is no debate that D.B. suffers developmental delay, D.B.'s contemporaneous medical records do not attribute his developmental delays to his infantile spasms. Rather, D.B.'s occupational therapist, Ms. Nicholas, consistently recorded in D.B.'s occupational therapy records that his developmental delays were consistent with his Down syndrome and further complicated by his ongoing reflux. (Ex. 3, *passim*.) However, during the hearing she testified:

> Q. Sure. So can you attribute any of [D.B.]'s delays -- developmental delays that he experienced after June 2014 to his episode of infantile spasms that ended in March of 2014?

> A. I can't point to anything specific. I felt that he would have been further along in his development at his current rate of development prior to the seizures compared to his rate of development after the seizures.

(Tr. 186.)

D.B.'s pediatrician, Dr. Leland, similarly provided a letter in which he stated: "It is probable, although it cannot be proven scientifically, that [D.B.], at 6 months after onset of infantile spasms, had additional developmental delays beyond those which would have been associated with his Down's syndrome." (Ex. 9.) Dr. Leland deferred to a specialist for any further insight into D.B.'s developmental trajectory. (*Id*.)

Standing alone, these opinions constitute unsubstantiated suspicion given the inability to identify any particular lingering deficits, albeit from individuals with professional knowledge of child development. A more comprehensive opinion seeking to substantiate that suspicion was provided in this case by neurodevelopmental pediatrician, Dr. Harum, who sought to demonstrate D.B.'s post-infantile spasms caused a developmental shortfall compared to his peers largely by calculating developmental quotients. However, Dr. Harum's opinion is not persuasive.

Dr. Harum sought to calculate developmental quotients for D.B. demonstrating his added delay following onset of infantile spasms. Specifically, she indicated that from 6.5 months of age to 16 months of age, D.B.'s developmental quotient dropped from around 77/61 to below 50. (Ex. 16, p. 2.) Critically, however, for the developmental quotients she calculated for 6.5, 8, 10, and 16 months, she did not disclose in her report the basis for those calculations. (Ex. 16, p. 2.) During the hearing, she was not able to explain the basis for those calculations. (Tr. 33.) In fact, the vast majority of the specific skills for which Dr. Harum calculated developmental quotients based on specific documented milestone were documented at 32 months of age and later and lack sufficient analogues from earlier periods to be helpful. (Ex. 16, pp. 2-3 (chart).) Dr. Harum confirmed that many of the developmental quotients presented in her reports relate to specific, individual skills, and that she did not have sufficient data to create a holistic developmental quotient for the entire relevant period. (Tr. 32-33, 38-40, 50-53.) She noted that these individual developmental quotients are "not a summary of his global development." (Tr. 33.) Although the Bayley Scales measure global development, the only available Bayley Scale measure for D.B. was at 42 months, at which time Dr. Harum agrees D.B. was on track relative to his Down syndrome peers. (Ex. 16, p. 1; Tr. 19, 33-34.)

Additionally, even those specific skills for which Dr. Harum provided some basis appear to lack reliability. For example, she testified that D.B. first walked at a normal age for a child with Down syndrome (within his third year of life). (Tr. 16-17 (discussing Malak et al., *Delay in Motor Development in Children with Down Syndrome,* 21 MED. SCI. MONIT. 1904-1910 (2015) (Ex. 18).) However, she considers this evidence of D.B.'s delay because the developmental quotients she calculated for him earlier in life suggest that he potentially may have walked as early as late in his second year of life. (Tr. 17.)

Yet, when discussing the relevant literature, she nonetheless acknowledged that "development is not evenly predictable." (Tr. 18.) Moreover, as noted above, Dr. Harum was not able to substantiate the basis for her earlier developmental quotients prior to 32 months, which formed the premise for her assessment.

Dr. Harum also confirmed in testimony that a drop in the developmental quotient does not in itself indicate a regression. (Tr. 51.) Moreover, the literature Dr. Harum provided to support her opinion broadly suggests that (1) developmental scales, such as the Bayley scales, should not be used for predictive purposes (Ex. 59, p. 8.); (2) that it is well established that Bayley scores for children with Down syndrome drop significantly from the first to the second year of life (Ex. 59, pp. 6-7); and (3) developmental quotients are inherently limited in that all children, including those with Down syndrome develop at different rates, especially where other factors such as D.B.'s hearing loss may be factors. (Layton, *Developmental Scale for Children with Down Syndrome,* (2004) (Ex. 57, p. 1).). Dr. Harum herself acknowledged that developmental quotients generally, at least those pertaining to intellect, are less reliable for children under two years of age due to the many factors involved. (Tr. 40.) She also acknowledged that developmental quotients for children with Down syndrome in particular are also known not to be stable for children under two years of age. (Tr. 17-19 (discussing Niccols & Latchman, *Stability of the Bayley Mental Scale of Infant Development with High Risk Infants,* 48(1) BRIT. J. OF DEVELOPMENTAL DISABILITIES, 3-13 (2002) (Ex. 19).) Thus, Dr. Harum's overall approach to this case also appears to have broader methodologic limitations.

In contrast, Ms. Nicholas confirmed, based on her first-hand account of D.B.'s ongoing occupational therapy, that D.B. not only regained his milestones within six months, but also that he had resumed making progress beyond his prior baseline. (Tr. 186.) Especially because of the substantial limitations in Dr. Harum's use of developmental quotients, this appears to be the best evidence of record regarding the status of D.B.'s recovery. Coupled with the medical evidence demonstrating his quick neurologic recovery within that time, this suggests that neither D.B.'s infantile spasms nor any developmental barriers related to his infantile spasms, persisted beyond six months. This is further supported by Dr. Kinsbourne's and Dr. Holmes's broader discussion, noted above, regarding the expected outcomes for infantile spasms as well as Dr. Holmes's more detailed discussion of the factors that contribute to whether the effects of infantile spasms will be temporary or permanent. Dr. Harum's opinion reveals that the further question of how D.B. would compare to his peers but for his infantile spasms involves a substantial degree of speculation.[46] And, in any event, Dr. Harum ultimately opined that "[p]utting into perspective the somewhat typical development trajectory for Down syndrome, it appears that D.B. is not markedly different from his [Down syndrome] peers . . . ." (Ex. 16, p. 3.)

[46] To be clear, this decision does not doubt the utility of developmental quotients to the field of developmental pediatrics nor suggest it is unreasonable to cite or rely on developmental quotients in all contexts. The issue here is that petitioner's use in this case appears to extend that tool beyond its acknowledged limitations to answer a question more precise and more granular than developmental quotients are intended to address.

Petitioners also filed a small study by Tapp et al., purporting to compare neurodevelopmental outcomes among children with Down syndrome and infantile spasms against those with Down syndrome without infantile spasms. (Tapp et al., *Neurodevelopmental outcomes in children with Down syndrome and infantile spasms,* 13(2) J. PEDIATR. NEUROL. 74-77 (2015) (Ex. 61.)) However, this study is not persuasive. With only eight subjects, it is very small. In fact, the authors acknowledged that the study size is inadequate to capture the full spectrum of outcomes. (*Id.* at 4.) Moreover, although the authors indicate that the *mean* developmental quotient was twenty points lower for the infantile spasms group, the authors did not provide the full range of developmental quotients for the control group, making it still more difficult to assess the spectrum of outcomes. (*Id.* at 3.) Additionally, the authors acknowledge that they failed to control for socioeconomic factors that could affect neurodevelopment and also did not have a homogenous group with regard to onset and duration of seizures. (*Id*. at 4.) And, in any event, there's no question that infantile spasms have the potential to have longstanding effects on childhood development. That is apparent from Drs. Kinsbourne's and Holmes's discussion of the condition. However, they also testified that infantile spasms can have good outcomes, suggesting that the overall conclusion of this study is not indicative of individual outcomes.

ii. Swallowing and fine motor deficits

Dr. Harum did also indicate that D.B. has "residual deficits in L[eft] hand ability and in oropharyngeal motor skills that affect his feeding in a pervasive way." (Ex. 16, p. 3.) While this is true, there is not preponderant evidence that either of these specific deficits is related to D.B.'s infantile spasms.

In fact, D.B.'s medical records attribute his feeding difficulties to low tone and motor weakness related to his Down syndrome. (Ex. 14, *passim*.) Additionally, the literature relied upon by Dr. Harum indicates that 40% of children with Down syndrome will experience onset of poor oral motor skills by 21-25 months of age. (Layton, *supra,* at Ex. 57, p. 4.) Moreover, D.B.'s occupational records indicate that he had impaired oral motor abilities from the time of his first assessment. (Ex. 3, p. 20.) During the hearing, Dr. Harum confirmed that the post-infantile spasms swallowing and choking difficulty she identifies is the same problem D.B. experienced pre-infantile spasms, only worsened. (Tr.54-55.) Dr. Harum did not explain how infantile spasms could lead to such consequence; however, to the extent she identified it as a motor issue (Tr. 42-43), Dr. Holmes disagreed that a motor problem is a likely consequence of infantile spasms. (Tr. 285-86, 340). In contrast, Dr. Harum acknowledges motor delays generally, as well as swallowing difficulties specifically, are associated with Down syndrome. (Tr. 46-47, 54-55.)

With respect to residual left-hand deficits, Dr. Harum was similarly unable to persuasively explain how this could be a consequence of infantile spasms. Specifically, she testified:

> Q. What is your physiological basis for treating a focal injury to the left upper extremity in January of 2017 to infantile spasms that occurred in February of 2014?
>
> A. It's just a natural maturation of that neuronal injury. It sometimes takes a while for, again, a developmental milestone to be anticipated and, yet, not achieved, and then also, I think maturity of the actual neuronal injury. There can be ongoing inflammation after the injury as well that can perpetuate neurological dysfunction. There certainly is no other explanation.

(Tr. 42.)[47]

Dr. Holmes explained, however, that infantile spasms lead to issues of higher cortical function, which affect memory, language, learning and executive function. (Tr. 285-86.) He stressed that conditions like cerebral palsy or white matter disease are not consequences of infantile spasms. (*Id*.) According to Dr. Holmes, motor function is not a concern when treating infantile spams. (Tr. 285-86, 340.) Dr. Holmes also indicated that a fine motor deficit in particular would be unusual as a sequela of infantile spasms. (Tr. 352-53.) Dr. Holmes also explained that the condition of infantile spasms represents a diffuse abnormality and, absent the type of comorbid focal lesion present among the Carrazana subjects (*see* Carrazana et al., *supra,* at Ex. 92), it would not be expected to result in unilateral focal deficits. (Tr. 286-88.) Based on Dr. Holmes's review of D.B.'s EEG studies, nothing in D.B.'s own history is suggestive of a focal pathology. (Tr. 287-88.) Dr. Kinsbourne likewise agrees there is no focal injury in this case. (Tr. 221.)

iii. Weight gain due to ACTh treatment

Finally, there is evidence to suggest that D.B. gained an unusual amount of weight following his ACTh treatment. (*See* ECF No. 108, p. 3 (listing weight measurements from medical records).) Moreover, temporary weight gain is an acknowledged side effect of ACTh treatment. (Tr. 335-37.) According to petitioner, D.B. never lost this weight *per se*; however, as he continued to grow his weight did eventually normalize again relative to his expected growth. (Tr. 254-55.) Mr. Bangerter testified that the added weight was beginning to resolve by D.B.'s first birthday, but petitioner testified it was still evident at about 18 months of age. (Tr. 111-12, 250.) However, if D.B. experienced ACTh-related weight gain that persisted for more than six months, a remaining question is whether this constitutes any complication or residual effect of D.B.'s alleged vaccine injury within the meaning of the Vaccine Act.

Recently, the question of what it means under the applicable statutory language to "suffer" a "residual effect or complication" of a vaccine-related injury was addressed

[47] As previously noted, although Dr. Harum stressed that she has a strong background in neurology and neuroscience, when asked if she has ever practiced as a neurologist, she indicated "not as you conceive of neurology, no." (Tr. 21.) Moreover, Dr. Harum was presented by petitioner as an expert in pediatrics and pediatric development rather than as an expert in neurology. (Tr. 7.)

by the Federal Circuit in *Wright v. Secretary of Health and Human Services*, No. 2021-1524, 2022 WL 38987 (Fed. Cir. Jan. 5, 2022). The Circuit confirmed that determining whether something constitutes a "residual effect or complication" of a condition begins with establishing proximate causation pursuant to the same test used for determining causation-in-fact. That is, the condition must be a "but for" cause and "substantial contributing factor," even if it is not the sole or predominant cause. *Wright*, 2022 WL 38987 at *4 (citing *Shyface*, 165 F.3d at 1352). The Circuit further explained that while a "residual effect" must be residue of the condition or injury at issue, a "complication" may be something caused by the injury or condition that is not "essential" to the condition and may be "outside the ordinary progression of the vaccine injury." *Wright,* 2022 WL 38987 at *5-6. Thus, for example, although they did not reach the question, the Circuit left open the possibility that necessary testing or diagnostic procedures might in some contexts constitute a complication or residual effect. *Id*. at *7. The Circuit further stated that "such procedures could cause somatic changes that are 'complications' within the meaning of 42 U.S.C. § 300aa-11(c)(1)(D)(i)." *Id*. It is therefore likely that a side effect caused by treatment of the injury at issue could satisfy the Vaccine Act's severity requirement even if the resolution of the injury itself occurs within six months of vaccination.

Importantly, however, the Circuit did not suggest that *any* somatic effect would be sufficient to meet the statutory requirement. The Circuit also stressed the requirement within the statutory language that a complication or residual effect must be something that is "suffered." *Id*. at 5. The Circuit explained that Congress intended for only "serious injuries" to be compensated and therefore the term suffered should be interpreted "to require painful or otherwise detrimental effects." *Id*. at 6. Thus, the fact that the testing at issue in *Wright* was non-invasive factored into the holding that the severity requirement was not met in that case in the absence of any lingering somatic effects from the injury itself. *Id.* Here, weight gain is a somatic effect; however, even if D.B.'s temporary weight gain did not go unnoticed, the record does not support the notion that it was painful, detrimental, or representative of any serious injury as contemplated by the statute.

While petitioner contends that D.B.'s weight gain interfered with his developmental progress (ECF No. 108, p. 1), there is not preponderant evidence to support that contention. During the hearing, petitioner did testify that she felt D.B.'s weight contributed to his not wanting to move around and not wanting to roll over during therapy. (Tr. 255-56.) However, when D.B.'s occupational therapist testified on the same subject, she acknowledged the weight gain, but attributed D.B.'s lack of cooperation to his fussiness and irritability, noting that it was difficult to soothe him. (Tr. 166-67, 186; *See also* Ex. 3, pp. 33.) Although this irritability was also likely attributable to the ACTh treatment (Tr. 335-37), petitioner testified that it resolved within several months of completing the ACTh treatment. (Tr. 250). Ms. Nicholas's daily notes repeatedly reference D.B. being fussy and irritable from March 6, 2014 through May 8, 2014, and thereafter do not mention fussiness again until December 18, 2014, at which point D.B. is noted to be suffering from a stomach bug. (Ex. 3, pp. 26-35, 67.) Weight is never mentioned in these records as a factor affecting the therapy sessions.

Accordingly, while D.B.'s weight gain was likely a "complication" of his alleged injury that persisted for more than six months, under the terms of the Vaccine Act it is not itself something that was "suffered" such that it could satisfy the statute's severity requirement.

VI. Conclusion

With the benefit of hindsight, it is clear that D.B. has had a good recovery from his infantile spasms. Nonetheless, it is also clear that he and his family experienced a harrowing period until that outcome became evident. For that, they have my sympathy. I also understand, given the facts of this case, why petitioner came to suspect D.B.'s vaccinations as the cause of his infantile spasms. For all the reasons discussed above, however, there is not preponderant evidence that any of D.B.'s vaccines caused or contributed to his infantile spams. There is also not preponderant evidence that complications or residual effects were suffered, within the meaning of the Vaccine Act, for greater than six months. Accordingly, petitioner is not entitled to compensation. Therefore, this case is dismissed.[48]

IT IS SO ORDERED.

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

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