In the United States Court of Federal Claims

No. 02-469V

(Filed: March 4, 2009)

CHRISTOPHER and CARLA LOVING, PARENTS of CAMILLE LOVING,	)	Vaccine case; Off-Table claim; significant aggravation of prior symptoms; required elements of proof; causation
Petitioners,	)	
v.	)	
SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES,	)	
Respondent.	)	

William Dobreff, Dobreff & Dobreff, Warren, MI, for petitioners.

Melonie J. McCall, Trial Attorney, Torts Branch, Civil Division, United States Department of Justice, Washington, D.C., for respondent. With her on the briefs were Michael F. Hertz, Acting Assistant Attorney General, Timothy P. Garren, Director, Vincent J. Matanoski, Acting Deputy Director, and Catharine E. Reeves, Assistant Director, Torts Branch, Civil Division, United States Department of Justice, Washington, D.C.

OPINION AND ORDER[1]

LETTOW, Judge.

Petitioners, Christopher and Carla Loving, seek review of a decision by a special master dated October 6, 2008, denying them compensation under the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, § 311, 100 Stat. 3743, 3755 (1986) (codified, as amended, at 42

[1]In accord with the Rules of the Court of Federal Claims ("RCFC"), App. B, Rule 18(b), this opinion and order is initially being filed under seal. By rule, the parties are afforded fourteen days in which to propose redactions.

U.S.C. §§ 300aa-1 to -34) ("Vaccine Act"). The Lovings have brought this claim on behalf of their daughter Camille. They allege that Camille's injection with a diphtheria, tetanus, and acellular pertussis ("DTaP") vaccine resulted in a significant aggravation of her infantile spasms.[2]

This is a so-called off-Table case in which the claimant must establish causation in fact.[3] The special master denied relief to the Lovings on the ground that they had "failed to establish that the return of Camille's infantile spasms happened at a time that was medically appropriate following the vaccine." *Loving v. Secretary of the Dep't of Health & Human Servs.*, No. 02-469V, 2008 WL 4692376, at *10 (Fed. Cl. Spec. Mstr. Oct. 6, 2008) ("Entitlement Decision"). Specifically, the special master concluded that Camille began to suffer from infantile spasms too quickly after receiving the DTaP vaccine. *Id*. For the reasons set forth below, the court concludes that the special master erred in ruling that the petitioners had failed to establish the temporal-relationship prong needed to prove causation. In particular, the special master failed to account for the facts that the DTaP vaccine was contraindicated for Camille and that the significantly aggravating injury that she suffered after her vaccination was precisely what was apprehended by the contraindication. Moreover, Camille's adverse reaction occurred promptly but not immediately after vaccination, and the medically accepted time for such occurrences indicates a 72-hour maximum but no minimum. Secondly, the special master also concluded that a prompt adverse reaction would have been accompanied by a systemic reaction to the vaccination and that Camille, in fact, did not have such a reaction. However, there was no evidence to support such a finding because, incredibly, Camille was neither examined nor treated by the attending physician or nurse after her adverse reaction began to occur, and thus no one evaluated whether or not she had or was having a systemic reaction.

BACKGROUND AND PROCEDURAL HISTORY

Infantile spasms, known also as West Syndrome, are a paroxysmal disorder that most commonly manifests itself in children less than a year old. *See* John H. Menkes, et al. *Child Neurology* 877 (7th ed. 2006). The medical profession classifies infantile spasms as a form of

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[2]An alternative form of this vaccine contains whole-cell pertussis antigens and is commonly designated as "DTwP." That type of DTP vaccine is no longer available in the United States. *See* PX 45 at 545 (Centers for Disease Control and Prevention, *Travelers Health: Yellow Book* (2005-06)) ("*CDC Yellow Book*").

[3]In accord with the Vaccine Act, the Secretary of Health and Human Services maintains a Vaccine Injury Table by regulation. *See* 42 C.F.R. § 100.3 (2008), as adopted and revised pursuant to the authority of 42 U.S.C. § 300aa-14(c). "The Table lists symptoms and injuries associated with each listed vaccine and a timeframe for each symptom or injury." *de Bazan v. Secretary of Health & Human Servs.*, 539 F.3d 1347, 1351 (Fed. Cir. 2008). If a listed symptom occurs after vaccination within the times specified, causation is presumed. *Id*. Injuries not listed on the Table or injuries suffered outside the specified times following vaccination are deemed off-Table injuries, and causation is not presumed. *Id*.

generalized epilepsy. *Id*. Infantile spasms are divided into two categories: cryptogenic or symptomatic. *Id*. Cryptogenic infantile spasms reflect an inability of doctors to identify a triggering cause for the resulting seizures. *Id*. When the cause of the infantile spasms is known, they are identified as symptomatic. *Id*. at 877-78. The vast majority of infantile seizures are classified as symptomatic. *Id*. at 877. Approximately half the children who experience infantile spasms will stop having seizures by age three or will instead suffer from Lennox-Gastaut Syndrome or from "major motor" seizures. *Id*. at 878. Infants who suffer from infantile spasms often are developmentally challenged. *Id*.

Camille Loving was born on August 2, 2000. Entitlement Decision at *1. Camille began to suffer from infantile spasms in January 2001. *Id*. Both parties agree that Camille suffered from infantile spasms prior to receiving her third DTaP vaccination in March 2001. *Id*. When Camille began to suffer infantile spasms, she was placed on medication that sought to limit the frequency and intensity of her seizures. *Id*. Camille proved to be responsive to Sabril, and with that medication her seizures markedly decreased to the point where Camille had not had clinical seizures for a period of 56 consecutive days. Tr. 36:21 to 38:13 (Test. of Dr. Robert M. Shuman, one of Camille's treating physicians and petitioners' expert), 457:24 to 462:15 (Shuman). As the special master noted, the degree of improvement and permanence of the improvement were disputed by the parties. Entitlement Decision at *1.[4]

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[4]As the petitioners' expert testified:

> [T]he seizures don't go away all at once. They step down in number, intensity, frequency, and duration. This was a marked step down.
> Q. But she wasn't seizure free?
> A. No, she wasn't seizure free.

Tr. 462:11-15 (Shuman).

The government's expert testified on cross-examination:

> Q. Before Sabril was instituted this child was having multiple cluster seizures per day. True?
> A. That's what's documented on the chart.
> Q. Okay. After Sabril started, within four days you're not having any cluster seizures at any position is noted. True?
> A. That is correct.
> Q. Then after the DTaP, the child's back to having cluster seizures again, multiple per day?
> A. That is also correct. However, there is no documentation from March, or in between other than the video EEG, that the child isn't having seizures.
> Q. Okay.
> A. And indeed the video EEG demonstrates the child still is having seizures.
> Q. Actually it demonstrated one seizure. True?
> A. Seizure is still a seizure.
> Q. All right. But under your definition you would say that a child who

On March 27, 2001, Camille "received the third dose of the DTaP vaccine." Entitlement Decision at *1. The DTaP Vaccine was contraindicated, *see, e.g.*, Tr. 362:12-15 (Shuman); 658:3-4 (Test. of Dr. Michael Kohrman, respondent's expert), because it risked aggravating Camille's infantile spasms. Tr. 450:2-5. The manufacturer of the DTaP vaccine informed prospective users that "the presence of a personal history of convulsion or an evolving disorder affecting the central nervous system is considered warning against further immunization with this vaccine." Tr. 361:17-21 (Shuman). The manufacturer of the vaccine also stated that infants who have "a recognized possible potential underlying neurologic condition" may begin to experience symptoms of "the underlying neurologic disorder within two or three days following whole-cell pertussis vaccination." Tr. 657:12-17 (special master's question to Kohrman, reading from PX 107 at 1501 (*Physician Desk Reference: Tripedia* (2003))). That warning is echoed by the *Yellow Book* issued by the Centers for Disease Control and Prevention ("CDC") which states that

> [C]ertain infrequent adverse events following pertussis vaccination are considered precautions (not contraindications) to additional doses of pertussis vaccine: a seizure, with or without fever, occurring within 3 days of immunization; temperature > 40.5°C (> 105°F) not resulting from another identifiable cause within 48 hours of immunization; collapse or a shock-like state (hypotonic-hyporesponsive episode) within 48 hours of immunization, or persistent, inconsolable crying lasting > 3 hours and occurring within 48 hours of immunization.

PX 45 at 547 (*CDC Yellow Book*).

Approximately five minutes after receiving the vaccination Camille "started having clusters of infantile spasms again." Entitlement Decision at *3. Camille first experienced the renewed onset of seizures while she was still in the doctor's office and being dressed by her mother after the vaccination. *See id*. Despite the fact that the seizure occurred at the doctor's office, there is no indication that the attending physician or nurse performed a physical examination after Camille experienced her seizure. Tr. 664:17 to 665:6 (Kohrman). The only contemporaneous account of the seizure is contained in Mrs. Loving's journal which recites the

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> had, say 10 cluster seizures a day for 14 days beforehand gets on the medication, Sabril, those stop, the only seizure that exists is a one to two-second event recorded on an EEG, while under 24[-hour] monitor by a physician. They then go to a DTaP shot, and within minutes after that this child's having multiple cluster seizures again. True?
>
> A. She had a cluster after the DPT that was described by mom. After that, the clusters, again, are not well-described in terms of their frequency.

Tr. 606:11 to 607:13 (Test. of Michael Kohrman).

onset of the seizure but no contemporaneous examination or treatment. *See* Entitlement Decision at *3.

After the vaccination on March 27, Camille began to experience one to two cluster seizures a day, each of which lasted several minutes. Petrs.' Mot. for Review and Mem. of Objections ("Petrs.' Mot.") at 4. Prior to receiving the vaccination, Camille allegedly experienced less than one electrical, but not clinical, seizure per month and that seizure typically would last only a few seconds. *Id*. Due to the increased frequency and intensity of the infantile spasms that Camille experienced, her development has likely been permanently impaired. Entitlement Decision at *1. Although Camille has stopped experiencing seizures, her mental capacity will likely continue to resemble that of a one-year old for the rest of her life. *Id*.

In his entitlement decision, the special master concluded that "the decisive element is the timing." Entitlement Decision at *3. The Lovings presented expert testimony by Dr. Robert Shuman, who also was serving as one of Camille's treating physicians, *see* Tr. 171:23 to 172:4,[5] that the five-minute interval between Camille's vaccination and the onset of her seizures was medically supportive of causation. Entitlement Decision at *4. In explanation of his opinion, Dr. Shuman testified that medical studies confirmed "that the DTaP vaccination can cause a resumption in infantile spasms within approximately five minutes." *Id*.[6] Dr. Shuman opined that the five-minute interval between the start of Camille's seizures and the administration of the vaccine was a medically reasonable time frame because Camille had a toxic reaction as contrasted to an immune-mediated reaction to the DTaP vaccine. *Id*. at *4. Dr. Shuman explained that "[t]he DTaP vaccine contained some amount of endotoxin and other components that could, in some dose, have a toxic effect. Some (or all) of the vaccine is picked up and transported within the circulatory system to the brain." *Id*. at *8 (citations omitted). Both Dr. Shuman and the government's expert agreed that "[t]he circulatory system moves blood throughout the body in approximately one minute." *Id*. (citations omitted).

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[5]Dr. Shuman is board certified in neurology with special competence in child neurology. Tr. 13:9-11 (Shuman). He received a bachelor's degree from Cornell University and a medical doctorate from Stanford University's Medical School. Tr. 14:7-10 (Shuman).

[6]The special master noted that all of the studies discussed by the parties involve patients that received "the whole cell pertussis vaccine" while Camille was administered "the acellular pertussis vaccine." Entitlement Decision at *5 n.4. The special master explained that Dr. Shuman's "analysis assumes that if the whole cell pertussis vaccine were reported to cause a significant aggravation of infantile spasms in five minutes, then the acellular pertussis vaccine could do so also." *Id*.

The government's expert, Dr. Michael Kohrman,[7] opined that Dr. Shuman's reliance on the relevant medical studies was misguided because the medical literature demonstrated that an adverse reaction to the vaccine took longer than five minutes to manifest itself. Entitlement Decision at *4. In addition, Dr. Kohrman suggested that the biological process that Dr. Shuman proffered as an explanation for the five-minute interval between the onset of the seizures and the administration of the vaccine did not occur in this case. *Id*. Dr. Kohrman stated that the process outlined by Dr. Shuman "produces a systemic response," and since "Camille displayed no evidence of a systemic response," the proposed biological mechanism was not implicated. *Id*.

After hearing the testimony of the two experts and reviewing their qualifications, the special master concluded that "[n]either their appearance on paper (as reflected in their curriculum vitae) nor their appearance at the hearing differentiate Dr. Shuman and Dr. Kohrman in any meaningful sense." Entitlement Decision at *4. In his view, both were qualified and credible witnesses. As the special master observed, "[b]oth parties' presentations were strong." *Id*. at *10. In the circumstances, the special master decided it would be appropriate to review "the literature on which the expert[s] relied" in determining whether the onset of infantile spasms within five minutes of the DTaP vaccine was medically reasonable. *Id*. at *4. After review, the special master concluded that the medical literature failed to establish "by a preponderance of the evidence, that vaccinations can cause infantile spasms, regardless of whether the infantile spasms are new or a resumption of previously experienced spasms, within five minutes." *Id*. In reaching that conclusion, the special master evaluated three of the articles on which the petitioners relied to support their argument that five minutes was a medically reasonable time. *Id*. at **5-7. He determined that the only support that the articles cited for such a rapid onset of infantile spasms after the administration of a vaccine was a 1948 study conducted by Randolph Byers and Frederick Moll. *Id*. at **6-7. As the special master commented, the paucity of recent studies is explained by the warnings instituted over the years against using pertussis vaccines with young children who have had infantile spasms. *See id*. at *8.

The fifth individual examined in the 1948 study experienced a twenty-minute interval between the administration of pertussis vaccine and the onset of symptoms of drowsiness, unresponsiveness, rigidity, and febrility. Entitlement Decision at *6. However, the 1948 study was not targeted to focus on infantile spasms and instead sought to examine "'any degenerative disease of the brain.'" *Id*. at *6 (quoting Dorland's Illustrated Medical Dictionary at 610 (30th ed. 2002)). The special master then sought to determine whether the patient in the fifth case study experienced infantile spasms after the administration of the vaccine, and he concluded that "[i]t [was] more likely than not that the fifth case [did] not describe an episode of infantile spasms." *Id*. at *7. In support of his conclusion, the special master cited to the fact that the patient "became 'drowsy'" and did not experience myoclonic seizures, which often accompany

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[7]Dr. Kohrman received a bachelor's and master's degree from Stanford University and a medical doctorate from Rush Medical College in Chicago. At the time of his testimony, he was Associate Professor of Pediatrics and Neurology at the University of Chicago. Resp.'s Ex. B; Tr. 237:18-19 (Kohrman).

the onset of infantile spasms. *Id*. The special master did not review any of the other case histories reported in the 1948 study because the next smallest interval between vaccination and the onset of symptoms was one hour. *Id*. The special master concluded that it would not be medically acceptable to infer causation because the length of time before the onset of symptoms in the 1948 study was significantly greater than that experienced by the petitioners' daughter in this case. *Id*.

The special master also considered the petitioners' experts' biological mechanism, which sought "to explain how the acellular pertussis vaccine could cause Camille to resume having seizures within five minutes." Entitlement Decision at *8. According to Dr. Shuman, the vaccine that was administered contained "endotoxin[s] and other components that could, in some dose, have a toxic effect." *Id*. Dr. Shuman opined that the presence of the endotoxins in the vaccine activated Camille's reserve of cytokines and caused them to travel to her brain. *Id*. at *9. Cytokines are often associated with the onset of seizures and are rapidly activated when the body encounters a foreign substance. *Id*.

Both experts accepted petitioners' proposed biological mechanism as a medically appropriate postulate, but they disagreed whether it occurred. Entitlement Decision at **8-9. The experts agreed that the "activation of cytokines causes other generalized effects." *Id*. at *9. Although there is no evidence in the record of Camille's general condition immediately after her vaccination because she was not then examined by a doctor or nurse, the special master concluded that Camille did not exhibit "any signs of a systemic reaction after her vaccination." *Id*. On this basis, the special master found that the petitioners' proposed biological mechanism did not occur in Camille's case. *Id*. at **9-10. Overall, the special master determined that Camille's resumption of infantile spasms manifested itself too soon to be caused by the DTaP vaccination, and denied recovery. *Id*. at *10.

Petitioner filed a Motion for Review of the special master's entitlement decision on November 4, 2008, and the government filed its response on December 4, 2008. This court held a hearing in this case on January 14, 2009. Thereafter, at the court's request, the parties submitted supplemental briefs focused on the evidence of record whether or not Camille had exhibited a systemic reaction after her vaccination, or, indeed, whether after her vaccination she was examined by a physician or nurse who could have detected the existence of signs of a systemic reaction. Accordingly, the case is now ready for disposition.

STANDARD FOR REVIEW

The Vaccine Act defines the review by this court of decisions by special masters in vaccine cases:

> (2) Upon the filing of a motion [to review a special master's decision], the United States Court of Federal Claims shall have

> jurisdiction to undertake a review of the record of the proceedings and may thereafter –
>
> . . .
>
> (B) set aside any findings of fact or conclusion of law of the special master found to be arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law and issue its own findings of fact and conclusions of law.

42 U.S.C. § 300aa-12(e)(2).[8] The Vaccine Act requires this court to analyze conclusions of law made by a special master to determine whether they are "not in accordance with law." *Id*. Factual findings by a special master may be set aside if they are found to be arbitrary or capricious or if a special master has abused his or her discretion in making such findings. *See id*. The Federal Circuit has commented that "[i]f the special master has considered the relevant evidence of record, drawn plausible inferences and articulated a rational basis for the decision, reversible error will be extremely difficult to demonstrate." *Hines v. Secretary of the Dep't of Health & Human Servs.*, 940 F.2d at 1518, 1528 (Fed. Cir. 1991).

ANALYSIS

In adopting the Vaccine Act, Congress sought to "establish a Federal 'no-fault' compensation program under which awards can be made to vaccine-injured persons quickly, easily, and with certainty and generosity." H.R. Rep. No. 99-908, at 3 (2d Sess. 1986), *reprinted in* 1986 U.S.C.C.A.N. 6334, 6344. To pursue its goals of a generous remedial program, Congress established a Vaccine Injury Table.[9] When a petitioner "[b]ring[s] [a] case within the timetable and specifications of a Table [i]njury and the statute does the heavy lifting – causation is conclusively presumed." *Hodges v. Secretary of the Dep't of Health & Human Servs*., 9 F.3d 958, 961 (Fed. Cir. 1993). For a petitioner to be able to avail themselves of the Vaccine Injury Table, the claimant must "establish that [he or she] received a listed vaccine and experienced such symptoms or injuries within the specified timeframes." *de Bazan*, 539 F.3d at 1351.

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[8]Prior to 1989, the judges on this court had the option of either "adopt[ing] the findings of the special master as its own judgment, or mak[ing] a de novo determination of any matter and issu[ing] its judgment accordingly." Randall B. Keiser, *Deja Vu All Over Again? The National Childhood Vaccine Injury Compensation Act of 1986*, 47 Food & Drug L.J. 15, 23 (1992). The statute was amended in 1989 to eliminate the ability of the judges on this court to review any portion of the special master's decision de novo. *See* Omnibus Budget Reconciliation Act of 1989, Pub. L. No. 101-239, § 6601(h), 103 Stat. 2106, 2289 (codified at 42 U.S.C. § 300aa-12(e)).

[9]The initial Vaccine Injury Table was published at 42 U.S.C.§ 300aa-14(a). The Table can be revised by the Secretary of Health and Human Services acting pursuant to notice-and-comment rulemaking under the authority of 42 U.S.C. § 300aa-14(c). The current version of the Vaccine Injury Table, as amended, is set out at 42 C.F.R. § 100.3.

However, if a petitioner is unable to bring a claim that comes within the scope of the Table, the individual is required to prove causation-in-fact by a preponderance of the evidence. 42 U.S.C. §§300aa-11(c)(1)(C)(ii), -13(a)1(A); *Althen v. Secretary of Health and Human Servs.,* 418 F.3d 1274, 1278 (Fed. Cir. 2005). The Federal Circuit has held that the causation-in-fact standard employed in off-table vaccine cases "is the same as 'legal cause' in the general torts context." *de Bazan*, 539 F.3d at 1351 (citing *Shyface v. Secretary of the Dep't of Health and Human Servs.,* 165 F.3d 1344, 1352 (Fed. Cir. 1999)). This standard requires a petitioner who brings an off-table claim to show that the vaccine was "'a substantial factor in bringing about the harm.'" *Id.* (quoting *Restatement (Second) of Torts* § 431(a) (1965)). The Federal Circuit has explained that in off-table cases "the heavy lifting [of proving causation] must be done by the petitioner, and [that burden] is heavy indeed." *Hodges*, 9 F.3d at 961.

The DTaP vaccine is listed on the Vaccine Injury Table. *See* 42 C.F.R. § 100.3(a). However, infantile spasms were, but are not now, listed on the Vaccine Injury Table.[10]

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[10]The original, statutory Vaccine Injury Table listed a seizure disorder occurring within three days of vaccination with DTP vaccine as a Table injury. *See* 42 U.S.C. § 300aa-14(a). However, in 1995, the Table was amended to remove that listing. *See Revision of the Vaccine Injury Table*, 60 Fed. Reg. 7678 (Feb. 8, 1995). The removal was made on the basis of two reviews and reports by the Institute of Medicine ("IOM"), one entitled "Adverse Effects of Pertussis and Rubella Vaccines," dated August 27, 1991, and a second entitled "DPT Vaccine and Chronic Nervous System Dysfunction: A New Analysis," dated March 2, 1994. The second IOM report took into account a study by D. L. Miller, N. Madge, J. Diamond, J. Wadsworth, and E. Ross, *Pertussis immunization and serious acute neurological illness in children*, 307 British Med. J. 1171-76 (1993) ("Miller Study").

The removal was controversial at the time. As the rulemaking notice indicated:

> In reviewing the Miller study, the IOM Committee reached three conclusions:
>
> (a) *The evidence is insufficient to indicate whether or not DTP increases the overall risk in children of chronic nervous system dysfunction*.
>
> (b) The balance of evidence is consistent with a casual relation between DTP and the forms of chronic nervous system dysfunction described in the NCES in those children who experienced a serious acute neurologic illness within 7 days after vaccine.
>
> (c) The evidence remains insufficient to indicate the presence or absence of a casual relation between DTP and chronic nervous system dysfunction under any other circumstances.
>
> After extensive review and discussion, the NVAC [National Vaccine Advisory Committee] subcommittee agreed with the IOM's conclusion that children who experience serious, acute neurological events after DTP vaccination can go on to exhibit "chronic nervous system dysfunction." The NVAC subcommittee concluded that *despite the conclusions of the*

Therefore, the petitioners have sought redress for the worsening of their daughter's infantile spasms through the compensatory provisions for off-Table injuries. Since Camille's infantile spasms predated her third DTaP vaccination, the petitioners' request for compensation is properly classified as presenting a significant-aggravation off-Table claim.

A. *The Elements of Proof for Significant-Aggravation Off-Table Claims*

Off-Table significant-aggravation cases are relatively rare. The special master commented that "[n]o appellate court has established the elements for this type of case." Entitlement Decision at *2. In light of the special master's perception that there was a dearth of binding authority, he applied the prevailing causation standard for an off-Table injury. *Id*. at *3.

> *Miller study, the information remains insufficient to accept or reject whether DTP administration prior to the acute, serious neurological event influenced the likelihood of neurologic dysfunction*. In order to avoid any confusion on this point, the Subcommittee approved the following summary statement:
> Children immunized with whole-cell DTP vaccines rarely experience acute, serious neurologic events that require hospitalization. An important question pertains to the long-term complications of these events. Among all children hospitalized with serious neurologic events, irrespective of their etiology or relationship to DTP, there is a potential for the presence of neurologic dysfunction when they are evaluated 10 years later. However, *the data are insufficient to accept or reject whether DTP administration prior to the acute, serious neurological event influenced the potential for neurological dysfunction*. *See* National Vaccine Advisory Committee (NVAC), Report of the Ad Hoc Subcommittee on Childhood Vaccines, p.7.

60 Fed. Reg. at 7684 (emphasis added).

The agency adopted "the IOM's conclusions and the NVAC subcommittee's evaluation of the IOM report, recognizing that questions will continue regarding DTP vaccine and chronic nervous system dysfunction." *Id*. at 7685 ("The Agency has determined that despite the uncertainty regarding causation, the final rule is consistent with both the IOM report and the NVAC subcommittee's conclusions regarding the Miller study."). The agency also addressed the differences between the 1991 and 1994 IOM reports and "an earlier 1985 IOM report which gave risk estimates for reactions following whole cell pertussis vaccination, and stated that pertussis vaccine causes permanent neurologic damage." *Id*. The agency commented that the 1985 IOM report was based upon a model to evaluate risks and benefits and the 1991 and 1994 reports were based upon "scientific literature on specific adverse events." *Id*.

As the agency said, "[t]he revised Table merely affects the presumption of causation available to certain petitioners. Petitioners will, of course, continue to have the option of proving causation by a preponderance of evidence if they are unable to prove a Table injury." 60 Fed. Reg. at 7682.

He recited that in *Althen* the Federal Circuit had explained that a petitioner's *prima facie* case when claiming an off-Table injury requires the individual "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 a proximate temporal relationship between vaccination and injury." *Althen*, 418 F.3d at 1278.[11] One judge on this court has expressed her agreement "with the special master in *Loving*, [that] the *Althen* analysis and other precedent related to new off-Table illnesses [is] applicable to cases involving the significant aggravation of an existing off-Table illness." *Doe/17 v. Secretary of Health & Human Servs.*, 84 Fed. Cl. 691, 701 n.13 (2008). Nonetheless, the Vaccine Act specifies that significant-aggravation and new-injury circumstances constitute separate avenues to potential recovery. 42 U.S.C. § 300aa-11(c)(1)(C)(i)-(ii); *see Shalala v. Whitecotton*, 514 U.S. 268, 274 (1995).

Notably, the precedents regarding significant-aggravation claims are not quite as sparse as the special master indicated. The Vaccine Act defines significant aggravation as "any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration of health." 42 U.S.C. § 300aa-33(4).[12] The Federal Circuit has stated that the definition of significant aggravation indicates that "the statute implicitly requires a comparison of the person's pre-vaccination condition with the person's current, post-vaccination condition. Indeed, such a comparison is inherent in the plain meaning of the word 'aggravation' itself." *Whitecotton v. Secretary of Health & Human Servs.*, 81 F.3d 1099, 1107 (Fed. Cir. 1996), *on remand from Shalala*, 514 U.S. 268.

On remand in *Whitecotton*, the Federal Circuit articulated a four-part test to govern significant-aggravation on-Table claims. 81 F.3d at 1107. The *Whitecotton* test requires the special master to

> (1) assess the person's condition prior to administration of the vaccine, (2) assess the person's current condition, and (3) determine if the person's current condition constitutes a 'significant aggravation' of the person's condition prior to vaccination within the meaning of the statute. If the special master concludes that the person has suffered a significant aggravation, the special master must then . . . (4) determine whether the first

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[11]The "proximate temporal relationship" has alternatively been described as a "medically-acceptable temporal relationship between the vaccination and the onset of the alleged injury." *Althen*, 418 F.3d at 1281.

[12]Congress stated that petitioners who bring significant aggravation claims cannot receive "compensation for conditions which might legitimately be described as pre-existing (e.g., a child with monthly seizures who, after vaccination, has seizures every three and a half weeks), but is meant to encompass serious deterioration (e.g., a child with monthly seizures who, after vaccination, has seizures on a daily basis)." H.R. Rep. No. 99-908, at 1 (2d Sess. 1986), *reprinted in* 1986 U.S.C.C.A.N. 6344, 6356.

symptom or manifestation of the significant aggravation occurred within the time period prescribed by the Table.

Id. Although the *Whitecotton* test was developed to address on-Table significant-aggravation claims, it has relevance in developing a test to govern off-Table significant-aggravation claims. The first three prongs of the *Whitecotton* test must be part of any standard used to evaluate the claim of a petitioner who presents a significant-aggravation claim, regardless of whether it is on- or off-Table. *See id*. (noting that the first two parts of the test "are practically inherent in the term 'aggravation'").

The fourth and last prong of the *Whitecotton* analysis is manifestly inapplicable to off-Table significant-aggravation claims because it was designed to address on-Table claims. *See Whitecotton*, 81 F.3d at 1107. Thus, the issue of causation and timing must be considered. In the context of on-Table claims, the Federal Circuit has stated that "[t]he statutory requirements to make out a *prima facie* significant aggravation claim are analogous to those required to make out a *prima facie* initial onset claim." *Id*. at 1103. Given the Federal Circuit's propensity for this symmetry in vaccine cases, *see id*., the *Althen* analysis of causation should also be applied in off-Table significant-aggravation claims, as the special master postulated. Accordingly, a petitioner who presents an off-Table significant-aggravation claim must prove by a preponderance of the evidence[13] that the vaccination caused his significant aggravation by offering: "(1) a medical theory casually connecting the vaccination and the [significant aggravation]; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the [significant aggravation]; and (3) a showing of a proximate temporal relationship between vaccination and [significant aggravation]." *Althen*, 418 F.3d at 1278. In short, the appropriate framework for determining whether a petitioner has made a *prima facie* showing that she has a compensable significant-aggravation off-Table claim is a combination of the first three prongs of the *Whitecotton* test with the three-part test articulated in *Althen*. The resulting six elements of proof for significant-aggravation off-Table claims thus become proof by a preponderance of the evidence of (1) the person's condition prior to administration of the vaccine, (2) the person's current condition (or the condition following the vaccination if that is also pertinent), (3) whether the person's current condition constitutes a "significant aggravation" of the person's condition prior to vaccination, (4) a medical theory causally connecting such a significantly worsened condition to the vaccination, (5) a logical sequence of cause and effect showing that the

[13]In *Althen*, the Federal Circuit stated that "close calls regarding causation are resolved in favor of injured claimants." 418 F.3d at 1280. However, in *Althen* the Federal Circuit emphasized "that a petitioner must prove causation in fact by 'a preponderance of the evidence.'" *Id*. at 1279 (referring to incorporation of the preponderance-of-the-evidence standard into the Vaccine Act at 42 U.S.C. § 300aa-13(a)(1)). The Federal Circuit has held that the preponderance of the evidence standard in the Vaccine Act means "more probable than not." *See Althen*, 418 F.3d at 1279 (citing *Hellebrand v. Secretary of the Dep't of Health & Human Servs.*, 999 F.2d 1565, 1572-73 (Fed. Cir. 1993)).

vaccination was the reason for the significant aggravation, and (6) a showing of a proximate temporal relationship between the vaccination and the significant aggravation.

If the petitioner is able to successfully put forward such a *prima facie* case, the burden shifts to the respondent to prove by a preponderance of the evidence that the petitioner's significant aggravation was caused by some factor other than the vaccine. 42 U.S.C. § 300aa-13(a)(1); *Althen*, 418 F.3d at 1278. With significant aggravation claims, "once a petitioner has made a *prima facie* case, the government may still prevail if it can show, to a preponderance of the evidence, that the pre-existing condition was, in fact, the cause of the individual's post-vaccination significant aggravation." *Whitecotton*, 81 F.3d at 1107. In addition, the government may be able to point to other factors apart from the preexisting condition that demonstrate the vaccine did not cause the significant aggravation. *See Althen*, 418 F.3d at 1278.

In this instance, although the special master did not apply the complete framework for evaluating the petitioners' claim as outlined above, he focused on one of the pertinent elements, *viz*., a showing by "preponderant proof that the [significant aggravation] occurred within a timeframe for which . . . it is medically acceptable to infer causation-in-fact." *de Bazan*, 539 F.3d at 1352 (citations omitted). The omission of findings on other elements does not impair the court's ability to review the special master's conclusions as to the one element that provided the basis for his decision.[14]

The special master's conclusion that the petitioners were unable to demonstrate "a proximate temporal relationship," *Althen,* 418 F.3d at 1278, was based on two findings. First, the special master, after reviewing the medical literature submitted by the parties, concluded that "the literature fails to establish, by a preponderance of the evidence, that vaccinations can cause infantile spasms, regardless of whether the infantile spasms are new or a resumption of previously experienced spasms, within five minutes." Entitlement Decision at *4. Secondly, the special master concluded that the petitioners' proposed biological mechanism did not occur in this case because he determined that there was no evidence that showed Camille suffered a systemic reaction that normally would accompany the proposed biological mechanism. *Id*. at *9.

B. *Temporal Relationship in Medical Literature*

Petitioners raise numerous objections to the special master's conclusion that they had failed to demonstrate that five minutes was a sufficient interval between Camille's vaccination

[14]In its supplemental brief, the government argues that the petitioners are not entitled to compensation "because [they] cannot demonstrate that Camille's condition was *significantly aggravated*" or "that the alleged vaccine-induced seizure was a *but for cause* or a *substantial factor* in bringing about Camille's current condition." Respt.'s Supplemental Br. at 8 (emphasis in original). Given that the special master did not address these issues in his entitlement decision, Entitlement Decision at *10, and because the case is being remanded to the special master, the court declines to address those issues at the present time.

and the resumption of her infantile spasms to infer that the vaccine was responsible for the significant aggravation. *See* Petrs.' Mot. at 10-20. Petitioners assert that the special master erred by "requiring [them] to produce articles showing infantile spasms or seizures [can] occur[] within five minutes after vaccination" and by failing to "consider[] that the vaccine was contraindicated." *Id.* at 10, 13. Petitioners assert that "[w]hen a contraindicated vaccine is used and the harm the contraindication is designed to prevent occurs and there is no alternate cause, petitioner[s] should receive compensation." Petrs.' Mot. at 15. In response, the government contends that the special master properly evaluated the evidence cited to support petitioners' contention that five minutes was an appropriate temporal period for an adverse reaction to occur and correctly concluded that "petitioners had failed to make a *prima facie* case on timing." Respt.'s Mem. in Resp. to Petrs.' Mot. for Review at 7 ("Respt.'s Mem."). However, respondent did not directly confront petitioners' contention that the special master failed to consider that the vaccine was contraindicated for Camille, given her history of infantile spasms.

In the particular circumstances of this case, the special master erred in relying on the absence of medical literature directly supporting the conclusion that a five-minute interval between Camille's vaccination and the exacerbation of her infantile spasms was a medically appropriate timeframe. Entitlement Decision at **1-2. Whether five minutes was a sufficient "timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact," *de Bazan*, 539 F.3d at 1352 (citations omitted), is a question that must be resolved on "the record as a whole." *See* 42 U.S.C. § 300aa-13(a)(1). Here, the special master failed to examine the record in its entirety when he determined that the petitioners could not satisfy the temporal-relationship prong of *Althen*.

Both experts, who were found by the special master to be well qualified, observed that due to Camille's preexisting infantile spasms and the significant chance that the DTaP would exacerbate her illness, medical literature recognized that the third dose of the vaccine that she received was contraindicated. *See, e.g.*, Tr. 170:6-12, 362:12-15 (Shuman), 658:3-4 (Kohrman). The experts' opinion that the vaccine was contraindicated was supported by the manufacturer's warning that "the presence of a personal history of convulsion or an evolving disorder affecting the central nervous system is considered warning against further immunization with [the DTaP] vaccine." Tr. 361:17-21 (Shuman). Indeed, as Dr. Shuman explained, all DTaP vaccines "clearly state that seizure[s] are a contraindication." Tr. 52:14-16, 54:18-22 (Shuman) (stating that "the two different types of [DTaP] vaccine which [Camille] received" had package inserts stating that her condition was a contraindication). Further, the contraindication of the third dose of the DTaP vaccination for Camille was supported by advisories issued by the American Academy of Pediatrics and the CDC. Tr. 361:2-13 (Shuman); PX 45 at 547 (*CDC Yellow Book*). Despite this extensive medical literature demonstrating that Camille received a contraindicated vaccine, the special master failed to address the implications of this salient fact in his entitlement decision.

This case was foreshadowed by the Federal Circuit's decision in *Capizzano v. Secretary of the Dep't of Health & Human Servs.*, 440 F.3d 1317 (Fed. Cir. 2006). In *Capizzano*, the petitioner alleged that her injection with a hepatitis B vaccine caused her to develop rheumatoid

arthritis. *Id*. at 1320. Petitioner presented the testimony of her four treating physicians that the hepatitis B vaccine was the cause of her rheumatoid arthritis. *Id*. at 1323. The special master did not credit that evidence because it was "based primarily on the temporal relationship between the vaccination and the onset of Ms. Capizzano's rheumatoid arthritis." *Id*. The special master's denial of compensation was vacated by the Federal Circuit. The court of appeals held that in appropriate circumstances the treating physicians' reliance on circumstantial evidence of "a logical sequence of cause and effect" was probative and would suffice to establish a prima facie case even where such evidence did not rise to the level of scientific or medical proof. *Capizzano*, 440 F.3d at 1325-26. In reaching its conclusion, the Federal Circuit explained that:

> if close temporal proximity, combined with the finding that hepatitis B vaccine can cause [rheumatoid arthritis], demonstrates that it is logical to conclude that the vaccine was the cause of the [rheumatoid arthritis] (the effect), then medical opinions to this effect are quite probative. Moreover, *Althen III* explained that medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether "a logical sequence of cause and effect shows that the vaccination was the reason for the injury."

Id. at 1326 (citations omitted). In *Capizzano*, the court of appeals added the cautionary note that:

> [t]here may well be a circumstance where it is found that a vaccine *can* cause the injury at issue and where the injury was temporally proximate to the vaccination, but it is illogical to conclude that the injury was actually caused by the vaccine. A claimant could satisfy the first and third prongs without satisfying the second prong when medical records and medical opinions do not suggest that the vaccine caused the injury, or where the probability of coincidence or another cause prevents the claimant from proving that the vaccine caused the injury by preponderant evidence.

Id. at 1327 (emphasis in original).

The special master's entitlement decision indicates that he thought the petitioners' case fell within the cautionary exception noted in *Capizzano*. However, the special master, by emphasizing so heavily the traditional medical literature that petitioners had produced, focused on evidence that was unresponsive to the precise factual question at hand. As Dr. Shuman observed, science does not "really have a good mechanism for the way in which pertussis creates seizures." Tr. 67:11-12 (Shuman); *see also Pafford v. Secretary of Health & Human Servs.*, 451 F.3d 1352, 1363 (Dyk, J. dissenting) (Because "scientific research on vaccine-related injuries remains incomplete[,] . . . it is not always possible to identify the 'medically accepted temporal relationship.'").

Here, both experts admitted that no medical studies exist examining the reaction of a child with infantile spasms to the contraindicated DPaT vaccine. Tr. 354:22 to 355:5 (Shuman);

626:20 to 627:15 (Kohrman). Such studies do not exist because it would be unethical for a doctor or anyone else to conduct them. Tr. 355:1-5, 679:1-9 (Shuman), 657:12 to 658:12 (Kohrman).[15] The only studies that do exist are relatively quite old and predate the contraindications and warnings. Those studies are not comprehensive because even the earlier literature disclosed that pertussis vaccine could cause rapidly ensuing harm if administered to a child suffering from infantile spasms. As the special master observed, "[f]ew articles are relatively recent. . . . [A]s medical science has learned that vaccines can cause adverse reaction, a standard of practice has developed not to administer an additional dose of a vaccine when an earlier dose of that vaccine may have caused an adverse reaction." Entitlement Decision at *8. That early experience taught that such adverse reactions to pertussis vaccine could occur within 72 hours after administration, establishing a maximum time for reaction but no minimum. *See supra*, at 4. Therefore, it is not surprising that neither the special master nor the experts were able to identify a study or a single case in the medical literature that addressed the present factual situation. Tr. 679:1-5 (Shuman).

The Federal Circuit has emphasized that a petitioner is not required to produce medical literature to support a claim for compensation, *Capizzano*, 440 F.3d at 1325; *Althen*, 418 F.3d at 1281, and the special master recited this principle. Entitlement Decision at *5. However, the special master ignored the principle when analyzing the petitioners' claim. By failing to address other evidence in the record which supported petitioners' claim, the special master in effect required petitioners to produce medical literature to support their position that five minutes was a medically appropriate interval between vaccination and the resumption of infantile spasms. In so doing, the special master overlooked that in this case "the use of [a] contraindicated vaccine resulted in the exact harm the contraindication was designed to prevent." Petrs.' Mot. at 14.

The Federal Circuit has stated that "the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field *bereft of complete and direct proof of how vaccines affect the human body*." *Althen*, 418 F.3d at 1280 (emphasis added); *see also Bunting v. Secretary of the Dep't of Health & Human Servs.*, 931 F.2d 867, 873 (Fed. Cir. 1991) (stating that "scientific certainty" is not the standard of proof in vaccine cases). Here, the special master focused solely on traditional (and older) medical literature to evaluate the claimed temporal relationship despite the fact that it was unresponsive to the extant factual situation. In so doing, the special master erred by ignoring evidence that demonstrates that the five-minute interval

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[15] As Dr. Shuman testified:

> Q. None of those [studies] were a study of a vaccination of a child with infantile spasms pre-existing and seeing what the effect is. True?
> A. Nobody would do that. No, they were not, and nobody would do that.
> Q. That group would be at a much higher risk to react?
> A. That group would be at a much higher risk to react, and it would be unethical.

Tr. 679:1-9 (Shuman).

between Camille's vaccination and the resumption of her seizures was a medically appropriate time to conclude that the vaccine was the cause-in-fact of Camille's worsened condition.

The package insert for the DTaP vaccine, which Camille received for her third shot, states that "[i]nfants and children with recognized possible or potential underlying neurologic conditions seem to be at enhanced risk for the appearance of manifestations of the underlying neurologic disorder within two or three days following whole-cell pertussis vaccination." PX 107 at 1501 (Package Insert for Tripedia); *see also* PX 106 at 1488 (Primary DTaP Vaccine Product Information).[16] In support of that conclusion, the manufacturers cite to a 1994 report of the Advisory Committee on Immunization Practices. PX 106 at 1497; PX 107 at 1507. One manufacturer also provided that "[c]onvulsions with or without fever, occurring within 3 days" is to be considered a warning against further vaccination with a DTaP vaccine. PX 107 at 1501; *see also* PX 45 at 547 (*CDC Yellow Book*) (providing that if a patient experiences "a seizure, with or without fever, occurring with 3 days of immunization" such an event should be treated as a "precaution" against further vaccination with DTaP).

Petitioners' expert explained that a manufacturer in developing a package insert has its medical staff examine published case reports, clinical experiences, vaccine adverse event profile reports, prior package inserts, and information about adverse reactions from a database. Tr. 346:13-17, 350:18-22 (Shuman).[17] The Food and Drug Administration ("FDA") has to approve and verify the information contained in the package insert before it can be published. *See* Tr. 351:1-8 (Shuman). Each package insert must contain a bibliography that is also vetted by the FDA. Tr. 351:9-14 (Shuman).

Medical literature submitted by respondents also supports the findings of the manufacturer that an adverse reaction to the vaccination typically will occur within three days of

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[16]The parties' experts disagreed whether Camille's infantile spasms constituted a progressive neurological disorder. *Compare* Tr. 205:11-14 (testimony of Dr. Shuman that infantile spasms are a progressive neurological disorder), *with* Tr. 657:6-11 (testimony of Dr. Kohrman that infantile spasms are not a progressive neurological disorder). Respondent's expert testified "that it [was] reasonable to go ahead and give the acellular pertussis to [Camille because] she does not have a progressive neurologic disease. And that would be the recommendation of the American Academy [of Pediatrics]." Tr. 656:24 to 657:3 (Kohrman). However, the CDC *Yellow Book* lists infantile spasms as an example of a progressive neurological disorder. PX 45 at 547. And, in contradiction of the statement of respondent's expert that the American Academy of Pediatrics would not have objected to the vaccination of Camille, the Academy advised physicians that the organization would recommend "considering deferral of immunization against pertussis in children with . . . [a] personal history of convulsion." PX 108 at 1512 (*Physician Desk Reference ACEL-IMUNE* (2001)).

[17]Petitioners' expert stated a manufacturing company's medical staff would include physicians, pediatricians, and epidemiologists. Tr. 350:18-20 (Shuman).

receiving the vaccine. *See* Respt.'s Ex. D at 67 (Institute of Medicine, National Academy of Sciences, *Adverse Effects of Pertussis and Rubella Vaccines*) (discussing a 1957 study by Baird and Borofsky where nine out of the twenty-four children they observed contracted infantile spasms "between 1 and 5 days after DPT vaccination"); *see also* Ex. 401 at 5 (Johannes C. Melchior, *Infantile Spasms and Immunisation in the First Year of Life* (1971)) (summarizing the interval between vaccination and the onset of infantile spasms reported in the medical literature). The summary of reported cases in the medical literature shows that onset of infantile spasms occurs relatively rapidly after the administration of pertussis vaccination. *See id*. In this respect, the manufacturers' warnings about potential adverse reactions to the DTaP vaccination do not indicate a minimum time for a reaction to the vaccination to manifest itself in an individual. Instead, the warnings establish that adverse events occurring within seventy-two hours of vaccination are typical. The special master did not evaluate articles that were consistent with the onset times set forth by the manufacturers because he was only interested in articles that showed that "a vaccine [could be] associated with the onset (or significant aggravation) of infantile spasms in an amount of time comparable to five minutes." Entitlement Decision at *7.

Respondent relies on the Federal Circuit's recent decision in *de Bazan* to support its claim that the petitioners failed to satisfy the temporal-relationship prong for causation. Respt.'s Mem. at 13-14. However, respondent's reliance on *de Bazan* is misplaced. In *de Bazan*, the petitioner experienced symptoms of acute disseminated encephalomyelitis ("ADEM") within eleven hours of receiving a tetanus-typhoid-diptheria vaccine. 539 F.3d at 1349-50. However, a model based upon animal studies indicated that it would take ten to fourteen days for symptoms of ADEM to appear after first receiving the vaccine. *Id*. at 1353. Based on this evidence, the Federal Circuit affirmed the special master's decision "that Bazan had not proven by a preponderance [of the evidence] that eleven hours is a medically acceptable timeframe within which ADEM could manifest after her vaccination." *Id*.[18] In the instant case, unlike *de Bazan*, the record evidence indicates that there is not a minimum time between vaccination with a contraindicated vaccine and the aggravation of a child's preexisting infantile spasms.

More generally, the Federal Circuit's recent decision in *de Bazan* credits the government's ability to disprove a petitioner's causation theory. *See* 539 F.3d at 1353. Thus, the government has the option to come up with medically or scientifically plausible explanations that

[18]The Federal Circuit so ruled even though *de Bazan* was "rechallenged" by the vaccine, having received the same vaccine on at least several prior occasions. The animal model appeared not to take into account rechallenge or sensitization situations.

seek to contradict the claimant's causation theory.[19] The presence of competing causal theories and a lack of knowledge about whether any of them occurred in a claimant often can produce close questions regarding whether a petitioner has established by a preponderance of evidence that the interval between vaccination and manifestation of symptoms occurred in a medically acceptable timeframe.[20]

In this case, the proofs related to the causal element are of a different character, and the issue of causation is not so close. The special master erred by failing to consider fully the implications of Camille's third DTaP vaccination having been contraindicated. By focusing principally on whether medical literature demonstrated that an adverse reaction to the DTP or DTaP vaccine could occur in an interval that was comparable to the one in this case, the special master lost sight of the teachings of *Capizzano*. The evidence demonstrates that the medically appropriate interval between vaccination and the resumption or onset of infantile spasms indicates a 72-hour maximum but no minimum. Thus, the petitioners established that the significant aggravation of Camille's infantile spasms occurred within a medically appropriate time after receiving the third DTaP vaccination. *See Capizzano*, 440 F.3d at 1326; *Althen*, 418 F.3d at 1279.

C. *Biological Mechanism*

In their initial filling with this court, petitioners alleged that the special master erred "by requiring [them] to prove a biological mechanism." Petrs.' Mot. at 9. In support of that contention, the petitioners cited to the special master's conclusion that the petitioners failed to persuasively establish "a mechanism that explains how the acellular pertussis vaccine could have

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[19]In the instant case, respondent's expert testified "that [Camille] had a viral illness with diarrhea 10 days prior to the onset of her spasm, that is a potential cause pre-existing to the onset of her spasms, and potential cause for her spasms." Tr. 610:6-9 (Kohrman). Respondent's expert admitted that "no tests were done to assess" what type of virus Camille had or what "bacterial or viral agent" caused the illness. Tr. 612:22-23, 613:19-22 (Kohrman).

[20]The logical, factually persuasive power of a petitioner's case can affect whether it is petitioner's or respondent's responsibility to address alternative causes. The Federal Circuit's decisions in *Walther v. Secretary of Health & Human Servs.*, 485 F.3d 1146, (Fed. Cir. 2007), and *Pafford*, 451 F.3d 1352, are illustrative. *Walther* sought to clarify that the majority's opinion in *Pafford* only required a petitioner "to eliminate potential alternative causes where the petitioner's other evidence on causation is insufficient." 485 F.3d at 1150. However, if "the other evidence on causation is sufficient to establish a *prima facie* case," then "the Vaccine Act does not require the petitioner to bear the burden of eliminating alternative causes." *Id*. This reworked approach has become the controlling interpretation of the discussion in the majority opinion in *Pafford* of petitioner's burden of disproving alternative causation in its *prima facie* case. *See de Bazan*, 539 F.3d 1352 & n.3.

caused Camille to have an infantile spasm within five minutes of receiving the vaccine." Entitlement Decision at *10. In response, the government asserted that the biological mechanism relied on by petitioners' expert was inapplicable to the present case because there was no indication that Camille suffered a systemic reaction, which would typically accompany the mechanism described, after she received her third DTaP vaccination. Respt.'s Mem. at 12-13.

At the entitlement hearing, petitioners sought to explain that Camille had a toxic reaction to her third DTaP vaccine. Dr. Shuman testified that Camille's third DTaP vaccine contained "[u]p to as much as 50 units [of endotoxins]." Tr. 352:13-20 (Shuman). He further explained that an "endotoxin is a specific activator of the blood brain barrier, that it is a rapid activator of disruption of the blood brain barrier, and that it is a small molecule, and that it is potent in extremely small amounts." Tr. 353:3-6 (Shuman). Dr. Shuman testified that the endotoxins contained in the DTaP vaccine had the potential to activate cytokines,[21] a substance that is capable of crossing the blood-brain barrier and causing the development of seizures. Entitlement Decision at *9. When the human body encounters a triggering agent it is able to rapidly produce cytokines. *See* Tr. 473:14 to 474:16 (Shuman); Entitlement Decision at *9. Given that the DTaP vaccine is transported by the circulatory system to the brain and that it takes approximately a minute for the circulatory system to distribute blood throughout the body, Tr. 329:4-12 (Shuman), the five minute-interval between Camille's vaccination and the resumption of cluster infantile spasms was reasonable since it would take at most a minute for the cytokines to reach the blood-brain barrier after they were produced. *See* Entitlement Decision at *8.[22]

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[21]Dr. Shuman explained that he used the term cytokines to encompass the various "chemical substances circulated in the blood which alter the blood brain barrier." Tr. 333:18-20 (Shuman).

[22]Dr. Kohrman generally accepted the biological mechanism proposed by Dr. Shuman but added two caveats. First, he suggested that the inclusion of an adjuvant in the vaccine would slow transport in the blood to the brain:

> Well, in order for the vaccine to get to an individual, as Dr. Shuman explained yesterday, to the brain, it's a double injection. It's in an adjuvant. Why is it an adjuvant? So it will stay in the muscle to give the body time to respond to it. So that the preparation doesn't leak out. And, yes, circulation time is six seconds, but this doesn't leak out immediately, number one. Number two, only small amounts leak out at a time because of the adjuvant in the vaccine preparation.

Tr. 560:23 to 561:8 (Kohrman). Dr. Kohrman's second caveat was that the action of cytokines would have been accompanied by a systemic reaction:

> Number two, for the kind of reaction to produce a seizure, break down a blood brain barrier in a toxic reaction, as Dr. Shuman implied, release of those chemotactic factors will set off a generalized response. Those leukotrienes, those cytokines don't just sit in the brain. They're going to go into the bloodstream.

The blood-brain barrier "is a wall interposed between that which is in the vascular system and that which is in the brain" and generally "protect[s] the brain from toxins circulated in the body." Tr. 330:19-23 (Shuman); *see also* Tr. 260:2-12 (Shuman). According to Dr. Shuman, Camille's blood-brain barrier was not operating at full strength because the seizures that she had experienced and her infantile spasms had damaged her blood-brain barrier. Tr. 334:2-6 (Shuman). Thus, the damage to the blood-brain barrier would allow toxins to more quickly migrate across the barrier into the brain. Tr. 335:1-10 (Shuman). Dr. Kohrman, while acknowledging that "acute seizures change [the] blood brain barrier," explained that the change is "a short-lived event related to a seizure" because MRI studies show that the changes in an individual's blood-brain barrier as a result of a seizure are not present twenty-four hours after the seizure. Tr. 648:19-25 (Kohrman).

In evaluating the petitioners' proposed biological mechanism, the special master identified a potential problem with the explanation provided by Dr. Shuman. Entitlement Decision at *9. Both of the experts testified that if the biological mechanism outlined by Dr. Shuman occurred in the instant case, Camille would have exhibited a systemic reaction to the vaccination. *See, e.g.*, Tr. 562:8-10 (Kohrman); 668:6-10 (Shuman). The special master concluded that the petitioners' biological mechanism was unpersuasive because the record did not indicate that Camille suffered a systemic reaction to her third DTaP vaccination. Entitlement Decision at *9. The special master concluded that because there was no indication that Camille suffered a systemic reaction, "she did not activate a large enough quantity of cytokines that would have been associated with some components of the acellular pertussis vaccine permeating her brain." *Id*.[23]

At the hearing on January 14, 2009, petitioners' counsel asserted that the special master's determination that Camille's lack of a systemic reaction established that the proposed biological mechanism did not occur was erroneous because no one examined Camille after she received the vaccination. Tr. 14:18 to 15:7 (Jan. 14, 2009). In light of this assertion, the court requested that the parties file supplemental briefs to address the evidence in the record as to whether Camille experienced a systemic reaction to her DTaP vaccination, or indeed, whether she was actually examined by medical staff after her vaccination. Order of Jan. 14, 2009 (Docket No. 120). Petitioners' submission contended that the lack of a physical examination of Camille after she

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> They are going to have a systemic effect.

Tr. 562:4-10 (Kohrman).

[23]A second problem identified by the special master revolved around the dispute between the parties' experts over "how quickly components of the DTaP vaccine enter the circulatory system." Entitlement Decision at *9. The special master found it unnecessary to resolve this dispute given his conclusion that "there has not been a showing that the endotoxin caused Camille to activate the cytokines." *Id*.

received her third DTaP vaccination establishes that "[t]here was no basis to determine a systemic reaction did not occur." Petrs.' Post Hearing Br. at 4. Petitioners emphasize "that Camille was dressed when the seizure occurred" and that her mother would be focused on the fact that Camille was experiencing seizures and not on whether the immunization site had a red hue. *Id*. at 4-5. Respondent counters by relying heavily on Camille's mother's journal entry for March 27, 2001, which describes Camille's having experienced a head-drop but reflects no additional annotations about her condition at the time. *Id*. at 3.[24] Thus, the parties are drawing opposing inferences from the fact that there is not a medically oriented description of Camille's condition after her third DTaP vaccination.

Neither party disputes that the medical records that accompanied Camille's third DTaP vaccination were not properly completed and are of no utility in determining whether Camille experienced a systemic reaction. *See, e.g.*, PX 10 at 237 (Royal Oak's Evaluation Form); Tr.

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[24]The only account of a percipient witness regarding Camille's seizure after her vaccination is contained in her mother's journal. *See* Respt.'s Supplemental Br. at 3. The relevant portion of the journal entry for March 27, 2001 states that:

> About 2 minutes after shots as I picked her up & dressed her-- Camille began to make a head dropping gesture that was very similar to a weakened spasm -- she did this 5-6 times & then stopped -- I took her into the hall to show the nurse who saw maybe the last one -- (No one's ever around when weird things occur!). I asked if she thought it was due to the trauma of the shots she said "you mean pain?" – Yes!

PX 29 at 345 (Mrs. Loving's Journal (Mar. 27, 2001)). The parties have tried to divine from the above quotation whether or not Camille suffered a systemic reaction to her vaccination. The government correctly notes that description contained in Mrs. Loving's account does "not indicate that Camille was hot to the touch, red in color, or had become limp." Respt.'s Supplemental Br. at 3. The absence of such an annotation is of limited utility because it shows merely that no such reaction was recorded, and not whether it occurred or did not occur. Also, by emphasizing the account in Camille's mother's journal the government seeks to rely on the reconstruction of the event by an individual who is not medically trained. During the time a systemic reaction would have appeared Camille's mother was focused on the fact that her daughter was experiencing a seizure and thus she was not evaluating whether her daughter exhibited signs of a systemic reaction. Tr. 678:15-19 (Shuman). The government's argument wrongly draws the conclusion that because there is no contemporaneous recitation of a systemic reaction, Camille must not have suffered such a reaction to her third DTaP vaccination.

Respondent emphasizes the fact that Mrs. Loving used the phrase "very similar" in her description and concludes from that description that Camille did not suffer a systemic reaction after receiving her third DTaP vaccination because she had not previously experienced a systemic reaction. Respt.'s Supplemental Br. at 3. However, such a parsing of the passage is unreasonable. Camille's mother used the phrase "very similar" to compare "the head dropping gesture" that her daughter was exhibiting at the moment to "weakened spasms" that she had seen Camille previously experience.

664:21-25 (Kohrman). The medical records that accompany Camille's third DTaP vaccination fail to show "what happened after the immunization." Tr. 664:23-24 (Kohrman); *see* PX 10 at 237 (Royal Oak's Evaluation Form). The medical form also gives no indication that Camille was examined by a doctor or nurse after she received the DTaP vaccine. *See, e.g.*, PX 10 at 237 (Royal Oak's Evaluation Form); Tr. 665:2-6 (Kohrman).

In support of his conclusion that Camille did not suffer a systemic reaction to her third DTaP vaccination, the special master also relied on a report by Camille's neurologist submitted almost two weeks after the vaccination. Entitlement Decision at *9. The record from Camille's visit to the neurologist, Dr. Harry T. Chugani, is unhelpful because the purpose of the visit was not to search for the reason why she experienced a significant aggravation of her infantile spasms within five minutes of the DTaP vaccination but rather was to examine her current status given her rapid deterioration after receiving the third DTaP vaccination and what could be done to prevent the further worsening of her condition. PX 11 at 239-41 (Summary of Camille's Visit to Children's Hospital of Michigan). Given that Dr. Chugani did not affirmatively search to determine the cause of why Camille experienced the resumption of infantile spasms within five minutes, his report simply does not address whether Camille suffered a systemic reaction to her third DTaP vaccination.

The special master and government both equate the fact that there is no evidence in the record indicating that Camille suffered a systemic reaction as evidence that she did not suffer such a reaction. Such reasoning is specious. The absence of evidence in the record concerning Camille's immediate reaction to her third DTaP vaccination does not mean that Camille failed to experience a systemic reaction to the vaccine. The absence of evidence in the record simply indicates that no one recorded Camille's reaction to her third DTaP vaccination except to note the seizure. Given that the special master's conclusion that Camille did not suffer a systemic reaction is based on the faulty logic of treating the lack of evidence in the contemporaneous medical record as confirmation that Camille did not suffer a systemic reaction, his finding that petitioner's biological mechanism did not occur in Camille's case due to the fact that she did not experience a systemic reaction must be set aside because his reasoning shows that "there has been a clear error of judgment." *Citizens to Preserve Overton Park, Inc. v. Volpe*, 401 U.S. 402, 416 (1971).[25]

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[25]The government argues that the special master's conclusion that Camille did not suffer a systemic reaction, if erroneous, would constitute a "harmless error" because the petitioners would not be able to show that it was "more probable than not that a systemic reaction occurred." Respt.'s Supplemental Br. at 7. However, the government's argument is misplaced because the lack of evidence of a systemic reaction was the only ground on which the special master relied in rejecting petitioners' proposed biological mechanism. Entitlement Decision at *9. Given that the petitioners are able to show that Camille's reaction to her third DTaP vaccine occurred within a medically acceptable time for such a biological mechanism, the special master's erroneous conclusion is prejudicial.

CONCLUSION

For the foregoing reasons, petitioners' motion for review is GRANTED, the decision of the special master dated October 6, 2008, denying compensation is VACATED, and the case is REMANDED to the special master for proceedings to determine whether petitioners can satisfy the required elements of a significant-aggravation off-Table claim. If petitioners establish a *prima facie* case, the burden passes to the respondent to show by a preponderance of evidence that Camille's illness was the result of some cause other than her DTaP vaccination. If petitioners prevail in these respects, the special master should proceed to determine whether compensation is due to petitioner, and if compensation is due, how much compensation is appropriate.

It is so ORDERED.

s/ Charles F. Lettow
Charles F. Lettow
Judge