

In the United States Court of Federal Claims

No. 02-1211 V
(Filed July 5, 2011)

WALTER RAY GRAVES, and)	
LISA GRAVES as Representatives)	
of the Estate of HAYLEY NICOLE)	Vaccine case; claims that death due to
GRAVES, Deceased,)	onset and intractability of seizures was
Petitioners,)	caused by Prevnar vaccine; causation
v.)	opinion of treating physician.
SECRETARY OF THE DEPT. OF)	
HEALTH AND HUMAN)	
SERVICES,)	
Respondent.)	

Richard Gage, Cheyenne, WY, for petitioners.

Lisa A. Watts, Torts Branch, Civil Division, United States Department of Justice, Washington DC, for respondent. With her on the briefs were *Tony West*, Assistant Attorney General, *Timothy P. Garren*, Director, *Mark W. Rogers*, Deputy Director and *Vincent J. Matanoski*, Assistant Director, Torts Branch, Civil Division, United States Department of Justice, Washington, DC.

OPINION AND ORDER

Merow, *Senior Judge*.

Following the death of their infant daughter Hayley, petitioners Walter and Lisa Graves seek review of decisions by a special master denying compensation under the National Childhood Vaccine Injury Act of 1986 (the “Vaccine Act”), 42 U.S.C. §§ 300aa-1 to -34. They allege that a Prevnar^{1/} vaccination on August 8, 2000, caused the onset of Hayley’s seizures two days later. She was hospitalized immediately and continually thereafter for twenty-nine days, primarily in pediatric

^{1/} Prevnar is the brand name of a pneumococcal conjugate vaccine covered under the Vaccine Injury Table. 42 C.F.R. § 100.3(a)(XII) (2008). Prevnar was licensed by the Food and Drug Administration (“FDA”) on February 17, 2000.

intensive care. Despite a battery of tests, treatment and examination by specialists, Hayley's seizures were unremitting and she died on September 24, 2000. Her death certificate documents the immediate cause of death as "[s]tatus epilepticus," and an underlying cause as "[i]ntractable seizures." (Pet. Ex. 4.) Neither Hayley nor her family had a prior history of seizures.

The special master determined that petitioners did not establish by preponderant evidence that the Prevnar vaccine administered to Hayley on August 8, 2000, caused the onset of the seizures that resulted in her death on September 24, 2000. *Graves v. Sec'y of HHS*, 2008 WL 4763730 (Fed. Cl. Spec. Mstr. Oct. 14, 2008) ("*Graves I*").

Petitioners timely filed a Motion for Review on November 13, 2008. Following the filing of a Response on December 12, 2008, and oral argument on February 10, 2009, by Order dated April 9, 2009 (ECF No. 101), the undersigned deferred review of the errors claimed, and remanded the matter to the special master for a supplemental decision. The remand order noted that, while disagreeing on whether Prevnar could and did cause Hayley's seizures, it appeared that the experts concurred that Prevnar could cause subsequent seizures to increase in duration. Hayley died because her seizures were intractable. The impact of Prevnar on the duration of seizures was neither addressed nor resolved by the special master in *Graves I*.

Putting aside the issue whether the administration of Prevnar vaccine can cause the onset of seizures, the record evidence raises a question whether the IL-1 beta in Hayley's system, stemming from the vaccine administration, served to "pre-prime" her system so as to render subsequent seizures (however caused), occurring within a reasonable time period, intractable or of sufficient duration to comprise a substantial causal factor for her death. The special master's decision does not address this question.

Remand Order, 2009 WL 989772, at *1 (Fed. Cl. Apr. 9, 2009). Subsequently, consideration of the then-recent Federal Circuit opinion in *Andreu v. Sec'y of HHS*, 569 F.3d 1367 (Fed. Cir. 2009) was also included in the supplemental proceedings. 2009 WL 1856461, at *1 (Fed. Cl. June 26, 2009).

Both parties filed supplemental expert reports. Following submission of additional medical articles and hearings, on September 21, 2010, the special master filed a Published Remand Decision Denying Entitlement. *Graves v. Sec’y of HHS*, 2010 WL 5830501 (Fed. Cl. Spec. Mstr. Sept. 21, 2010) (“*Graves II*”). Responding to the supplemental inquiries posed, the special master answered that the intractable nature of Hayley’s seizures and/or their duration comprised a substantial causal factor in her death. However, the special master concluded that petitioners failed to provide preponderant evidence that the Prevnar vaccine induced the production of an amount of IL-1 β that could have lengthened Hayley’s seizures. *Id.* at *9-10. Specifically, the special master questioned the reliability of the experimental evidence cited by petitioners’ experts to connect the Prevnar vaccine and extension of the duration of seizures. It was asserted that the evidence confirming extension of seizures involved doses of IL-1 β far exceeding the IL-1 β in Hayley’s system. *Id.* at *7-9. Finally, the special master concluded the Federal Circuit’s decision in *Andreu* did not alter his *Graves I* opinion. *Id.* at *10-12.

Following the remand decision, additional briefs were filed. After careful review of the extensive medical records, expert medical testimony, and research studies presented, together with the helpful oral argument of counsel, the court concludes that the special master erred in denying compensation. First, on the supplemental analysis requested, the court concludes the special master erroneously discredited medical research underlying the opinion of petitioners’ expert, Dr. Byers, that Prevnar can and did increase the duration of Hayley’s seizures. Secondly, in the special master’s initial entitlement decision, the burden of proof requirements imposed on petitioners were excessive. Errors included: (1) the focus on whether Hayley had a fever or other adverse reaction prior to the onset of seizures; (2) the weight accorded the testimony and opinion of Dr. James Wheless, Hayley’s treating pediatric neurologist; and (3) the discounting of medical studies upon which petitioners’ medical experts relied. The burden of proof bar was set too high. Accordingly, to the extent required, the court enters its own findings, and reverses the denial of compensation in *Graves II* and *Graves I*. The case is remanded to the special master for a determination of damages.^{2/}

^{2/} The intervening *Zatuchni* decision potentially expands the scope of recovery. *Zatuchni v. Sec’y of HHS*, 516 F.3d 1312 (Fed. Cir. 2008).

Facts

Hayley Graves was born on November 4, 1999 in Ft. Worth, Texas. When she was four months old, Hayley was treated for gastrointestinal distress by Dr. Melanie Harston, her pediatrician. Dr. Harston noted Hayley held her head to the right and was unable to move it to the left. Dr. Harston's assessment was torticollis.^{3/} She was referred to physical therapy for evaluation and treatment. Otherwise, no physical abnormalities were noted. (Pet. Ex. 1 at 16-18.) At her well-baby check-up when she was five months old no physical abnormalities were noted. She had attained all developmental milestones. Her torticollis and gastrointestinal problems had improved. Physical therapy would wait pending further observation. (*Id.* at 21.) On her six-month check-up, torticollis continued to be a concern; otherwise she met all developmental milestones. (*Id.* at 23.)

Records of her August 8, 2000 preventative health visit document that she was given Motrin for teething. It was noted that she “[did] not crawl or sit independently for long.” Dr. Harston's assessment was gross motor delay and she planned to have Hayley evaluated for physical therapy. (*Id.* at 31.) While petitioners disagree that Hayley's muscle development was delayed, neither the medical experts, the special master, nor the parties considered this to have been a contributing or relevant factor in the events that unfolded. In this regard, the record includes an August 8, 2000 photograph of Hayley sitting erect. (Pet'rs' Ex. 35.) At that August 8, 2000 appointment, at approximately 11:15 a.m., Hayley received a Hepatitis B and her second Prevnar vaccination.^{4/}

According to the affidavit of Hayley's mother, Lisa Graves, filed with the Petition in this matter, the remainder of August 8, 2000, Hayley acted normally. On August 9, 2000, she was restless and stayed awake until about 10:30 or 11:00 p.m. Early on the morning of August 10, 2000, Hayley woke up about 6:45 a.m. and, according to the affidavit: “she did not appear right. The left side of her body was moving and it would not stop. We called the doctor's office and waited for a return

^{3/} Torticollis is an “abnormal contraction of the muscles of the neck, producing twisting of the neck and an unnatural position of the head.” *Dorland's Illustrated Medical Dictionary* (31st ed. 2007) at 1967.

^{4/} Hayley received her first Prevnar vaccination on May 5, 2000. (Pet. Ex. 1 at 23.)

call; however, at 7:15 a.m. when we still had not heard back from the doctor's office, we left for Cook's Children[s] Medical Center.” (Pet., Lisa Graves' Aff. at 2.)

Medical records from the emergency room of the Fort Worth, Texas Cook Children's Medical Center reported that Hayley was crying, fussy and somewhat groggy. (Pet. Ex. 2 at 5, 9, 11.) She was given Ativan and fosphenytoin for seizures. Her Prevnar vaccination two days earlier was noted (*id.* at 8) as was the recent administration of Tylenol and Motrin. (*Id.* at 5.) An admission assessment of nurse Ginger McKee reported that Hayley had been given Motrin about 8 or 9 o'clock p.m. the prior evening, August 9, 2000. (Pet'rs' Ex. 9 at 109.) Her rectal (“R”) temperature was 38.2° Celsius at noon on August 10, 2000. (Pet. Ex. 2 at 10 and Ex. 9 at 23.)

Hayley was admitted and transferred to the pediatric intensive care unit (“PICU”) under the care of Dr. Brian Ryals, a pediatric neurologist. An EEG showed “ongoing electrical seizure activity emanating from right central brain regions.” (Pet. Ex. 2 at 15.) An MRI and CT scan were normal. (*Id.* at 1, 2.) Because barbiturate doses were prescribed, she was intubated, ventilated, and an arterial line was placed. She was continuously monitored and received regular doses of anticonvulsant medication, but her seizures did not stop. Serologic testing results were negative for infectious disease and for certain viruses. Medications given included phenobarbital, Depacon, Versed, Rocephin, Acyclovir, Topamax, Dilantin, valproic acid and Keflex. PICU medication logs included Tylenol. (Pet'rs' Ex. 9 at 235, 253, 41, 50, 55, 66, 94, 97, 98, 99.) Acetaminophen was given repeatedly starting on August 10, 2000. (*Id.* at 503-51.) The consultation report of Dr. Suzanne Whitworth recorded home medications of Motrin and Tylenol. (*Id.* at 106.) Hayley had a temperature of 38.1° Celsius (R) on August 24 and a “fever” on August 18. (*Id.* at 97, 62.) Medications included Tylenol as needed for fever. (*Id.* at 263.) The August 24, 2000 temperature was noted as significant. (*Id.*)

Hayley remained in intensive care until transferred to a “regular” room for about five days until noon on August 29, 2000, when she was airlifted to the Hermann Hospital Epileptic Center in Houston, Texas for evaluation and treatment by Dr. James W. Wheless,^{5/} Chief of Pediatric Neurology at the University of

^{5/} Noting that towards the end of her hospitalization at Cook Children's Medical Center and transfer on August 29, 2000, to Dr. Wheless at the Texas Comprehensive Epilepsy Program at Hermann

Tennessee College of Medicine, who later testified in these proceedings that Prevnar could and did cause her seizures and did so within a medically appropriate time.

For twenty-six days at Hermann Hospital, Hayley was evaluated by several specialists; multiple attempts were made to control her seizures without success. Tragically, her seizures which started the early morning of August 10, 2000, never stopped and Hayley died in the pediatric intensive care unit of the Hermann Hospital on September 24, 2000.

Hayley's death certificate recorded her cause of death as "[s]tatus epilepticus," caused by "[i]ntractable seizures." (Pet. Ex. 4.) An autopsy performed on September 29, 2000, concluded that Hayley "died as a result of hypoxic encephalopathy which reportedly occurred following a seizure which developed following a meningitis [sic] vaccine." (Pet. Ex. 6 at 6.)

Procedural Background

Dr. Wheless was concerned that the Prevnar vaccination was the cause for Hayley's death and he referred petitioners to the office of Richard Gage. (Tr. 272-74.) Petitioners filed a petition for vaccine injury compensation on September 16, 2002, alleging that Hayley suffered seizures and death as a result of receiving Prevnar and Hepatitis B vaccinations on August 8, 2000. The December 8, 2003, Respondent's Report recommended compensation be denied.

No substantive activity took place in the case for several years. On January 29, 2007, petitioners filed medical literature and an opinion from Dr. Vera Byers, an immunologist, presenting a medical theory that the Prevnar vaccine can initiate a cascade of biochemical effects that can culminate in seizures, with or without a fever, by activating the innate immune system (necessary for the vaccine to be effective)

Hospital in Houston, Texas, her left-sided seizures were almost constant, "[a]fter discussing with Dr. Wheless and him accepting for transport as well as the family agreeing, it was decided to transfer the patient to a comprehensive epilepsy center, and transport was arranged for her to go to Herman[n] Hospital in Houston, Texas (a distance of approximately 270 miles)." (Pet. Ex. 2 at 3 (parenthetical added).)

which in turn initiates the production of the cytokine^{6/} interleukin - 1 β (“IL-1 β ”) which can cause seizures. Prevnar is “capable of generating a biochemical and cellular cascade involving the cytokine IL-1 β which is a known trigger for seizures. This process would typically occur within a time frame of hours to 2-3 days. It may or may not be accompanied by fever.” (Pet’rs’ Ex. 17 at 6.)

Also on January 29, 2007, petitioners filed the opinion of Dr. Marcel Kinsbourne, a neurologist, that Prevnar, having been shown to cause seizures, with or without a fever, most likely caused the onset of seizures in Hayley which never stopped and lead to her death. “It is my opinion, to a reasonable degree of medical probability that the Prevnar vaccination, which Hayley Graves received when she was nine months old, caused, or significantly contributed to the causation of the severe refractory seizure disorder that caused her death. This is a causation-in-fact opinion.” (Pet’rs’ Ex. 15 at 4.) Dr. Kinsbourne reviewed Hayley’s medical history, Dr. Byers’ opinion, an article titled “Postlicensure Surveillance for 7-Valent Pneumococcal Conjugate Vaccine,” by Dr. Robert P. Wise, *et. al*, published in the *Journal of the American Medical Association* (“JAMA”) in 2004 (the “Wise study”) (Pet’rs’ Ex. 21), pre-licensing data and other information in the *Physician’s Desk Reference* (“PDR”) (Pet’rs’ Ex. 19) and the Pneumococcal Conjugate Vaccine (commonly used brand name of Prevnar) entry in Micromedex (Pet’rs’ Ex. 20) all discussed in detail hereinafter.

On December 26, 2007, petitioners filed a report from Hayley’s treating pediatric neurologist and pediatric epilepsy specialist, Dr. James W. Wheless, to whom Hayley was referred by the Cook Children’s Medical Center where she was initially presented through the emergency room. (Pet’rs’ Ex. 43.) Dr. Wheless later opined that:

Prevnar vaccine is known to cause seizures, both afebrile and febrile (without and with a fever) and these can be serious, and potentially even lead to death. It is my medical opinion that Hayley’s vaccine was associated with the onset of her seizures, which proved to be intractable and her acute encephalopathy, which then progressed to chronic

^{6/} Cytokines are proteins secreted by various cell types that regulate the intensity and duration of immune response and mediate communication between cells. *Stedman’s Medical Dictionary* (28th ed. 2000) at 487.

encephalopathy accompanied by an intractable seizure disorder, and ultimately this was fatal and responsible for her death. An extensive evaluation was performed, including obtaining her brain post-mortem, and after examining this no other cause could be found. It is established that Prevnar vaccine can contribute to this type of injury. Prevnar is established as causing this type of injury and, in this case, it is also my belief that the vaccine did cause this injury. I have also reviewed Dr. Kinsbourne's report and am in agreement with that.

It is my opinion, based on a reasonable degree of medical probability, that the Prevnar vaccination, which Hayley Graves received when she was nine months old, caused her severe refractory seizure disorder that caused her death. This is a causation-in-fact opinion and is based on my role as her treating physician and as an expert in the field of pediatric epilepsy.

(*Id.* at 2 (parenthetical supplied) (citation omitted).)

On April 27, 2007, respondent filed a report from Dr. Michael Kohrman, a pediatric neurologist. Dr. Kohrman reviewed the reports of Drs. Byers and Kinsbourne, and while concurring that animal studies showed IL-1 β increased the duration of seizures, Dr. Kohrman disagreed that the literature cited by Dr. Byers established that IL-1 β can cause seizures in the first instance. "This paper shows that the brain must have had prior convulsions for IL[-]1 β to have a direct effect on convulsions." (Resp't's Ex. C at 5.) Dr. Kohrman's February 12, 2008, supplemental report (Resp't's Ex. M) criticized Dr. Wheless' causation opinion as new – not reflected in the extensive contemporaneous treatment notes which are in the record. He also disagreed with Dr. Byers' mechanism opinion, reasoning that if IL-1 β was accumulating in Hayley's system as hypothesized, a reaction at the vaccination site or a fever would have been presented.

Expert medical testimony was taken at hearings on December 20, 2007, February 22, 2008, and July 21, 2008.

Graves I

In his October 14, 2008, Published Decision Denying Entitlement, the special master concluded petitioners failed to provide preponderant evidence that Prevnar could cause seizures in the absence of a fever. The special master examined the two articles cited by Drs. Wheless and Kinsbourne for their opinions that this vaccine could and did cause Hayley's seizures, the Wise post-licensure study and the PDR, discussed hereinafter. Disagreeing with these physician specialists, the special master concluded that "these two articles do not show that Prevnar causes seizures without a fever." *Graves I*, 2008 WL 4763730, at *6.

Dr. Byers also opined and testified that Prevnar can cause seizures in the absence of a fever. The special master concluded that Dr. Byers' opinion was not "persuasive" (*id.* at *5) because she relied on isolated portions of what he characterized as inapposite medical articles, and because Vaccine Act cases have "consistently" declined to award compensation for seizures not accompanied by a fever. The special master also limited Dr. Byers' opinion because of her reliance on animal, not human, experiments. To the extent her opinion that IL-1 β can cause seizures was supported by cited articles, her opinion was not as persuasive as Dr. Kohrman's response that to do so would require a high concentration, which would have resulted in a fever or other adverse reaction prior to triggering a seizure; accordingly, petitioners failed to provide preponderant reliable medical evidence that Prevnar can cause seizures in the absence of a fever. The special master did, however, comment that seizures can produce IL-1 β and IL-1 β can increase the duration of seizures.

The special master further concluded that petitioners had not proven by a preponderance of the evidence that the Prevnar vaccine caused Hayley's seizures. The special master noted that respondent's expert Dr. Kinsbourne, a professor of psychology, while a neurologist, rarely saw patients and has testified in "many, many cases in the Vaccine Program on behalf of petitioners." *Id.* at *5. Hayley's treating epilepsy specialist, pediatric neurologist Dr. Wheless, is frequently invited to speak at conferences worldwide, and Dr. Kohrman, respondent's expert, recognized his excellent reputation. *Id.* Nevertheless, Dr. Wheless' opinion that the Prevnar vaccine caused the onset of Hayley's seizures was rejected by the special master, asserting that it was not clear he held that opinion at the time he was treating Hayley, although his testimony was that while he was treating her, he suspected it and referred

petitioners to legal counsel.^{7/} Years later he was contacted by petitioners for his opinion, for which he was compensated. The special master concluded that compensation for his expert opinion changed Dr. Wheless' status from Hayley's treating physician to just one of the experts paid to testify. He stated that he did not intend to imply that compensation influenced his opinion, but "[i]n these circumstances, Dr. Wheless's opinion stands on the same ground as any other expert retained by a party in litigation." *Id.* at *6.

Finally, the special master concluded that petitioners failed to establish that the approximately forty-four hours from Hayley's vaccination to the initial onset of her seizures was medically supportable. In rejecting Dr. Byers' opinion that from forty-four to forty-eight hours was an appropriate time, the special master concluded that reactions to the innate immune system (such as Prevnar is designed to do) would result in an immediate severe systemic reaction such as anaphylaxis within minutes. *Id.* at *15.

Motion for Review

Petitioners' Motion for Review was filed on November 13, 2008 (ECF No. 93). Following briefing and oral argument, without resolving the Motion for Review, the case was returned to the special master for a "supplemental decision and resulting conclusion as to entitlement." As there appeared to be a consensus that the Prevnar vaccination could cause subsequent seizures to increase in duration and it was the intractability of Hayley's seizures which caused her death, the special master was requested to consider whether the Prevnar vaccination was a substantial causal factor of the intractability. *Remand Order*, 2009 WL 989772, at *2 (Fed. Cl. Apr. 9, 2009).

Accordingly, prior to resolving the pending issue raised by the petitioner's Motion for Review, that is, whether to sustain or set aside the special master's seizure onset decision, it is concluded that, pursuant

^{7/} Dr. Wheless testified that when he was treating Hayley, he "suspected [the Prevnar vaccine] as a potential cause" of her seizures and he referred petitioners to their counsel in this litigation. (Tr. 272-74.) Dr. Wheless theorized that the vaccine caused the central nervous system to attack itself. (Tr. 296-98.) In *Graves I*, the special master commented that this theory was unrelated to the causal mechanism advanced by Dr. Byers that Prevnar activated the innate immune system to produce and accumulate IL-1 β . 2008 WL 4763730, at *9.

to 42 U.S.C. § 300aa-12(e)(2)(c), a remand to the special master is required. A supplementary decision addressing whether the intractable nature of Hayley's seizures and/or their duration comprised a substantial factor in bringing about Hayley's death and, if so, whether the reaction to Prevnar vaccine in Hayley's system, was a substantial causal factor with respect to the intractability and/or duration of the seizures she suffered. Petitioners seek compensation for Hayley's death, not for the seizures, so that even if the special master's decision that the vaccine was not proven to cause the onset of Hayley's seizures were to be sustained, there would remain for resolution the question of vaccine causation for any increased seizure duration and intractability as related to Hayley's death. The remand proceedings will enable the special master to address fully this remaining issue. *See* 42 U.S.C. § 300aa-12(d)(3).

Id.

Subsequent remand proceedings before the special master included a fourth evidentiary hearing on February 19, 2010, with expert medical testimony, submission of medical literature and briefing.

Graves II

On September 21, 2010, the special master issued his decision on remand. *Graves v. Sec'y of HHS*, 2010 WL 5830501 (Fed. Cl. Sp. Mstr. Sept. 21, 2010) ("*Graves II*"). The special master accepted the parties' agreement that the intractability of Hayley's seizures caused her death, citing her death certificate. 2010 WL 5830501, at *5. The remaining issue was "did Prevnar cause Hayley's seizures to become intractable?" *Id.*

The special master found that at small levels, IL-1 β can have a beneficial effect; at higher levels, it has no effect; at even higher levels, it can cause a fever; and at even higher levels, it can extend the duration of seizures. The special master then attempted to determine where Hayley had been on this continuum, concluding that her clinical picture was inconsistent with having enough IL-1 β in her system to have caused her seizures to become intractable. "Because there is no evidence that Hayley had a fever, Hayley's production of IL-1 β was less than the amount of IL-1 β needed

to extend the duration of any seizure.” *Id.* at *10. Accordingly, the special master determined petitioners failed to establish preponderant evidence that the Prevnar vaccine caused Hayley’s seizures to last longer. The special master also concluded that *Andreu* did not warrant reconsideration of his findings and conclusions in *Graves I*.

Legal Standards

The Vaccine Act provides for recovery of two types of claims: table and off-table. “In a table claim, a claimant who shows that he or she received a vaccination listed in the Vaccine Injury Table (“table”), 42 U.S.C. § 300aa-14, and suffered an injury listed in the table within a prescribed period is afforded a presumption of causation.” *Andreu*, 569 F.3d at 1374. In an off-table case, such as Hayley’s, a petitioner must prove actual causation by a preponderance of the evidence. *See Moberly v. Sec’y of HHS*, 592 F.3d 1315, 1321 (Fed. Cir. 2010). To prove actual causation, a petitioner must “show that the vaccine was ‘not only a but-for cause of the injury but also a substantial factor in bringing about the injury.’” *Id.* at 1321-22 (quoting *Shyface v. Sec’y of HHS*, 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)). A petitioner satisfies this burden by providing what is referred to the three *Althen* prongs:

- (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. While a petitioner must satisfy all three *Althen* prongs, in making this showing, “evidence used to satisfy one . . . prong[] can[] overlap to satisfy another prong.”^{8/} *Capizzano v. Sec’y of HHS*, 440 F.3d 1317, 1326 (Fed. Cir. 2006).

^{8/} In *Capizzano*, petitioner satisfied the first and third prongs of *Althen*. 440 F.3d at 1326 (“[T]he first prong of the *Althen* III test was satisfied by the finding that the hepatitis B vaccine can cause RA [rheumatoid arthritis]. The third prong was satisfied by the finding that Ms. Capizzano’s RA appeared within days of receiving the vaccine.”) (citations omitted). The Federal Circuit concluded that the special master had “erred in not considering the opinions of the treating physicians who concluded that the vaccine was the cause of Ms. Capizzano’s injury.” *Id.*

The preponderant-evidence standard is “a simple preponderance, of ‘more probable than not’ causation.” *Althen*, 418 F.3d at 1279 (citing *Hellebrand v. Sec’y of HHS*, 999 F.2d 1565, 1572-73 (Fed. Cir. 1993)). This standard “simply requires the trier of fact to believe that the existence of a fact is more probable than its nonexistence.” *Moberly*, 592 F.3d at 1322 n.2.

Causation is determined on a case-by-case basis, with “no hard and fast per se scientific or medical rules.” *Knudsen v. Sec’y of HHS*, 35 F.3d 543, 548 (Fed. Cir. 1994). Circumstantial evidence may satisfy this burden and “close calls regarding causation are resolved in favor of injured claimants.” *Althen*, 418 F.3d at 1280.

While the arbitrary and capricious standard of review applies to factual findings, the special master’s conclusions of law are reviewed without deference. *Cedillo v. Sec’y of HHS*, 617 F.3d 1328, 1338 (Fed. Cir. 2010); *Munn v. Sec’y of HHS*, 970 F.2d 863, 870 (Fed. Cir. 1992) (instructing that “[i]ssues of law – constitutional imperatives, statutory construction, procedural requirements – come to [the Federal Circuit] for decision with little if any deference owed to or expected by the forums below”). Requiring medical certainty raises the evidentiary bar too high as a matter of law. *Andreu*, 569 F.3d at 1379-80 (reversing special master’s decision that petitioners were not entitled to compensation); *see also Lampe v. Sec’y of HHS*, 219 F.3d 1357 (Fed. Cir. 2000); *Hodges v. Sec’y of HHS*, 9 F.3d 958, 961 (Fed. Cir. 1993) (disagreeing with dissenting judge’s contention that the special master confused preponderance of the evidence with medical certainty). Upon establishment of a prima facie case for entitlement, the burden shifts to respondent to prove that the injury was caused by factors unrelated to the vaccination. 42 U.S.C. § 300aa-13(a)(1)(B); *de Bazan v. Sec’y of HHS*, 539 F.3d 1347, 1352 (Fed. Cir. 2008).

Contentions of the parties on remand (*Graves II*) – seizure duration.

A. The court’s remand order was not a final decision; accordingly, a separate motion for review from the special master’s response to that remand was not required.

Respondent’s Supplemental Memorandum in Response to Petitioners’ Post Remand Memorandum (ECF No. 145), asserts that petitioners’ assignments of error, filed in response to this court’s order for supplementary briefing on petitioners’ Motion for Review (ECF No. 93), were untimely for failure to file a motion for

review within thirty days of the September 21, 2010 special master’s remand decision in *Graves II*. Respondent cites 42 U.S.C. § 300aa-12(e)(3) and RCFC, App. B, Vaccine Rule 23(a).

Petitioners disagree, asserting that the thirty-day requirement in the Vaccine Rules of the United States Court of Federal Claims and the federal statute only applies to *final* decisions, not to a remand with instructions prior to resolution of the matters presented. Petitioners are correct. In relevant part, 42 U.S.C. § 300aa-12(e) provides:

(e) Action by United States Court of Federal Claims

(1) Upon issuance of the special master’s decision, the parties shall have 30 days to file with the clerk of the United States Court of Federal Claims a motion to have the court review the decision. If such a motion is filed, the other party shall file a response with the clerk of the United States Court of Federal Claims no later than 30 days after the filing of such motion.

(2) Upon the filing of a motion under paragraph (1) with respect to a petition, the United States Court of Federal Claims shall have jurisdiction to undertake a review of the record of the proceedings and may thereafter--

(A) uphold the findings of fact and conclusions of law of the special master and sustain the special master's decision,

(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, or

(C) remand the petition to the special master for further action in accordance with the court’s direction.

The Vaccine Rules similarly provide that a remand order is not necessarily final. “Unless otherwise specified in the remand order, the decision on remand

constitutes a separate decision for purposes of Vaccine Rules 11, 18 and 23, i.e., judgment automatically will be entered in conformance with the special master's decision on remand unless a new motion for review is filed pursuant to Vaccine Rule 23." RCFC, App. B, Vaccine Rule 28.1(b).

The court's remand order here was not a final decision. "[P]rior to resolving the pending issue," the special master was asked to examine whether Hayley was preprimed such that the Prevnar vaccine extended the duration and/or intensity of her seizures and issue a "supplemental decision." *Remand Order*, 2009 WL 989772, at *2. Judgment could not and was not automatically entered as *Graves I* remained for resolution. *Graves II*, 2010 WL 5830501, at *6 n.5 ("The October 18, 2008 decision found that the Graveses had not established that IL-1 β can cause seizures. This decision is the subject of the pending motion for review.").

Respondent retorts that if on remand the special master had awarded compensation to petitioners, concluding that the Prevnar vaccine caused the intractability of Hayley's seizures which caused her death, judgment could then have been entered unless respondent filed a timely Notice of Review. That however, is not the circumstance presented. Rather, a final judgment following *Graves I* was possible, the special master directing in the concluding lines that "[i]f a motion for review is not filed, the Clerk's Office is ordered to enter judgment in favor of respondent." *Graves I*, 2008 WL 4763730, at *17. In contrast, the special master on remand was responding, and providing in the concluding line of *Graves II*, that "[p]ursuant to Vaccine Rule 28.1(a), the Clerk's Office is instructed to deliver a copy of this decision to the assigned judge." *Graves II*, 2010 WL 5830501, at *12.

The supplemental decision of the special master in *Graves II* is encompassed in this review of *Graves I*, as provided by the court's remand order. Respondent's position a second Motion for Review was required is rejected.

B. The Special Master elevated petitioner's burden to establish a medically plausible theory that Prevnar can prolong seizures.

The court has carefully examined the special master's decision in *Graves II*, the extensive medical testimony, literature and arguments. The special master concluded that the Prevnar vaccine induces the production of IL-1 β , but not all

amounts of IL-1 β have negative effects. A small amount is beneficial and assists in creating the intended immunity from pneumonia^{9/} while higher doses have been shown in animal studies to extend the duration of seizures. *Graves II*, 2010 WL 5830501, at *7 (citing Dr. Byers' testimony and authorities recognizing the dose-dependent effects of other vaccines). In addition to criticizing the absence of studies on humans that IL-1 β can extend the duration of seizures, the special master noted respondent's expert Dr. Kohrman's general opinion that extended seizure duration resulted only from mega-doses of IL-1 β . So the question viewed by the special master was, assuming the animal data could be extrapolated to a human infant, how much IL-1 β could have caused Hayley's seizures to become intractable?

Petitioners presented evidence that low doses of IL-1 β can extend seizures citing testimony of Drs. Byers and Kinsbourne as well as several medical articles including Petitioners' Exhibit 70 (Teresa Ravizza, *et al.*, "Innate and adaptive immunity during epileptogenesis and spontaneous seizures: evidence from experimental models and human temporal lobe epilepsy," 29 *Neurobiology of Disease* 142 (2008) reporting on experiments on humans with chronic epilepsy. (Tr. 591, ECF No. 132.)

While discounting the Ravizza study as "far afield," the special master acknowledged that "on the surface," a 2008 Vezzani study,^{10/} Petitioners' Exhibit 69, relied upon by Drs. Byers and Kinsbourne, supported petitioners' duration theory. *Graves II*, 2010 WL 5830501, at *7. The 2008 Vezzani study concluded, based on extensive research on animal models, that IL-1 β , in amounts produced naturally (endogenously) in the body (such as, petitioners' claim, from the Prevnar vaccination given to Hayley), increases the duration of seizures already occurring.

^{9/} There is no dispute that the Prevnar vaccine is effective in producing the desired immunity which is accomplished, in part, by the production of the cytokine reactions at issue here. That the desired immunity may require more than one dose of Prevnar does not deny petitioners' point that Prevnar does cause the creation of IL-1 β , a finding adopted by the special master in *Graves II*. In contrast, in *Graves I*, the special master concluded that IL-1 β does not cause seizures; IL-1 β is produced by the body as a way to recover from a seizure. *Graves I*, 2008 WL 4763730, at *11 (citing Tr. 195-202 (Dr. Kohrman)).

^{10/} References in *Graves II* that this Vezzani study, Pet'rs' Ex. 69, ECF No. 121-1, was in 2006, are incorrect. It was published in 2008.

“The preapplication of IL-1 β in rodent brain, by using concentrations within the range of those endogenously produced by seizures, prolongs the duration of seizures induced by intracerebral injection of chemoconvulsant drugs. . . .” (Pet’rs’ Ex. 69 at 3, ECF No. 121-1.) This 2008 peer-reviewed article, described by Dr. Byers as the culmination of decades of research by Dr. Vezzani, a world-renowned pioneer in this field “identifying IL-1 beta as the main actor in the production of various kinds of seizures” (Tr. 444, ECF No. 132) relied on prior peer-reviewed publications. Dr. Byers cited this Vezzani article among others for her opinion that Plevnar can and did significantly contribute to the extension of the duration of Hayley’s seizures within a medically appropriate time.

The special master, adopting the “general” opinion of Dr. Kohrman, however, disagreed with the conclusion in the 2008 Vezzani “invited review”^{11/} that the concentration of IL-1 β applied to the experimental animals was within the endogenous range, finding “[a] preponderance of the evidence shows that IL-1 β can affect the duration of seizures only when the amount of IL-1 β exceeds what is produced endogenously.” *Graves II*, 2010 WL 5830501, at *10. The special master reasoned that greater-than-endogenous concentration of IL-1 β is necessary to prolong seizures sense because IL-1 β is a pyrogen (a fever producer); a build-up would produce a fever before something worse happened, and rejected the opinion of Dr. Byers as well as the Vezzani research to the contrary. The special master cited Dr. Kohrman’s opinion that if Hayley had produced enough IL-1 β to have extended the duration of her seizures, then she would have displayed some precursor adverse reactions such as a fever and she did not. “This lack of fever necessarily places Hayley on a point in the dose-response curve where IL-1 β is at a level below the amount necessary to extend the duration of any seizure.” *Graves II*, 2010 WL 4763730, at *9.

^{11/} An invited review, also known as a review article, consists of a detailed and comprehensive narrative analysis of recent or evolving developments in a specific topic. It serves to highlight important points that have been previously reported in the literature.

...

As its name implies, reviews are usually invited by the editor. Authors who are invited to provide a review article are acknowledged to have a particular expertise and extensive experience in that field.

Peh WCG, Ng KH, “Writing an invited review,” *Singapore Med. J.* 2010; 51(4); 271, <http://smj.sma.org.sg/5104/5104emw1.pdf>.

The court concludes the special master erred. First, the special master improperly elevated petitioners' burden of proof and the medical theory was wrongly discounted due to the asserted absence of human experiments. Secondly, even under the standard employed, the special master's re-analysis of medical studies was incorrect, rendering his factual findings arbitrary and capricious.

Petitioners' medical theory is that IL-1 β produced naturally (endogenously) by the human body from a Plevnar vaccine increases the duration of seizures. Causation was satisfied by Dr. Byers' expert immunological testimony based on credible peer-reviewed medical literature, and extensive animal studies that the injection into the brain of IL-1 β in concentration levels produced endogenously, increases the duration of seizures.^{12/}

^{12/} Dr. Byers explained the biological mechanism between IL-1 β and the prolonging of seizures (as well as the instigation).

[T]here is at least two ways that IL-1 beta is causing the seizures. The first is they feel that it produces damage to the blood-brain barrier, which allows proteins then, proteins and ions that are in the body and should not be in the brain, to get into the brain and partially damage the neurons.

But the other way is that it starts a cascade which results in abnormal calcium channels in the neurons, and the way he [the authors of *A novel non-transcriptional pathway mediates the proconvulsive effects of interleukin-1 β* - Pet'rs' Ex. 71, ECF No. 121-2] does that is he shows that IL-1 beta induces a molecule called ansmas which induces ceramide, which then phosphorylates SERK, which then induces. . . NR-2B, which results in the convulsions.

(Tr. 452, ECF No. 132.)

Mindful that Plevnar, which in 2000 when administered to Hayley had just been approved by the FDA, there simply is no requirement of definitive medical proof of biological mechanism or causation. The Federal Circuit held that: "requiring medical literature . . . contravenes section 300aa-13(a)(1)'s allowance of medical opinion as proof." *Capizzano*, 440 F.3d at 1324 (quoting *Althen*, 418 F.3d at 1280). That petitioners' burdens under the Vaccine Act do not require a medical theory is grounded in statutory language. *See* 42 U.S.C. 300aa-13(a)(1) ("the special master or court may not make . . . a finding [of causation] based on the claims of a petitioner alone, unsubstantiated by medical records or by medical opinion"). 440 F.3d at 1324 (denouncing the necessity of "either epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect").

This is not a case of flawed research methods or biological implausibility. There is no suggestion of skewed research methods or results. As demonstrated in the recent autism cases, expert medical opinions based on discredited medical theories or research may be found not to be reliable. However, in the autism cases, the key article upon which experts relied was discredited by the scientific community and co-authors later retracted its conclusion. See *Cedillo v. Sec’y of HHS*, 617 F.3d 1328, 1336-40 (Fed. Cir. 2010); *Hazlehurst v. Sec’y of HHS*, 604 F.3d 1343, 1347-51 (Fed. Cir. 2010). In contrast, it was the special master and respondent’s expert Dr. Kohrman who questioned the purposeful use of the adjective “endogenous” in the 2008 Vezzani study.^{13/} Stating that “the Graveses are required to show, by a preponderance of the evidence, the reliability and persuasiveness of their expert, Dr. Byers,” *Graves II*, 2010 WL 5830501, at *7, the special master concluded that it is biologically plausible that IL-1 β , triggered by the Plevnar vaccine, can extend the duration of seizures, and then questioned and independently revisited the merits of the findings in the 2008 Vezzani article that IL-1 β in amounts produced naturally (endogenously) would do so, concluding that petitioners’ medical theory was not supported by a preponderance of the evidence.

Ultimately, the Graveses have failed to show, by a preponderance of the evidence, that Plevnar induced the production of an amount of IL-1 β that could have lengthened Hayley’s seizures. A preponderance of the evidence shows that IL-1 β can affect the duration of seizures only when the amount of IL-1 β exceeds what is produced endogenously. Thus, any (small) amount of IL-1 β that Hayley produced in response to Plevnar was not sufficient to extend the duration of Hayley’s seizures. See tr. 624. Therefore, the answer to the Court’s question, which asked “whether the reaction to Plevnar vaccine in Hayley’s system, was a substantial causal factor with respect

^{13/} The special master’s conclusion that the Ravizza article was “far afield,” *Graves II*, 2010 WL 5830501, at *7, was not assailed by petitioners in post-remand argument. Dr. Byers did, however, testify to its relevance in depicting humans with chronic seizures as having elevated IL-1 β , which responds to criticism by the special master that studies on humans were lacking. (Tr. 450, ECF No. 132.) That the seizures there were caused by inflammation is not relevant for the point presented – that is seizures, however caused, produce IL-1 β . “IL-1 beta is produced by the inflammation and it causes additional inflammation.” *Graves II*, 2010 WL 5830501, at *7 (citation omitted). Dr. Byers did not testify that this article showed that IL-1 β prolonged the seizures and did not discuss the dosage of IL-1 β involved.

to the intractability and/or duration of the seizures she suffered,” is “no.”

Graves II, 2010 WL 5830501, at *10.

Subjecting research supporting an otherwise unassailed medical theory presented by medical experts with similarly unassailed credentials, to credibility review to measure preponderance, was, in this instance, inconsistent with precedent. The Federal Circuit has held that a special master may not require ““epidemiologic studies . . . or general acceptance in the scientific or medical communities”” because such prerequisites would ““impermissibly raise[] a claimant’s burden.”” *Andreu*, 569 F.3d at 1378 (quoting *Capizzano*, 440 F.3d at 1325-26); *see also Moberly*, 592 F.3d at 1325; *Althen*, 418 F.3d at 1280 (requiring a claimant to provide “medical literature” “contravenes section 300aa-13(a)(1)’s allowance of medical opinion as proof.”). Rather, a medical theory under Prong One of *Althen* can be established by expert medical testimony; “confirmation of medical plausibility from the medical community [n]or literature” is not required. 418 F.3d at 1279. *See Grant v. Sec’y of HHS*, 956 F.2d 1144, 1148 (Fed. Cir. 1992) (“evidence in the form of scientific studies or expert medical testimony is necessary [to demonstrate causation in fact];” *see also Andreu*, 569 F.3d at 1379 (“[A] paucity of medical literature supporting a particular theory of causation cannot serve as a bar to recovery.”)).

“Thus, for example, causation can be found in vaccine cases based on epidemiological evidence and the clinical picture regarding the particular [claimant] without detailed medical and scientific exposition on the biological mechanisms.” *Knudsen*, 35 F.3d at 549 (“The Vaccine Act does not contemplate full blown tort litigation in the Court of Federal Claims.”). Rather, ““petitioner[s] must provide a reputable medical or scientific explanation that pertains specifically to the petitioner’s case, although the explanation need only be “legally probable, not medically or scientifically certain.”” *Broekelschen v. Sec’y of HHS*, 618 F.3d 1339, 1345 (Fed. Cir. 2010) (citing *Knudsen*, 35 F.3d at 548-49). “[C]ausation in the medical community may require a much higher level of certainty than that required by the Vaccine Act to establish a prima facie case. The special master must take these differences into account when reviewing the scientific evidence.” *Broekelschen v. Sec’y of HHS*, 89 Fed. Cl. 336, 343 (2009), *aff’d*, 618 F.3d 1339 (Fed. Cir. 2010). In this regard, the Federal Circuit has counseled that special masters are not to delve into “research” reserved “for scientists, engineers, and

doctors working in hospitals, laboratories, medical institutes, pharmaceutical companies, and government agencies” by “ascertaining precisely how and why DTP and other vaccines sometimes destroy the health and lives of certain children while safely immunizing most others.” *Knudsen*, 35 F.3d at 549.

The thorough and well-reasoned recent opinions in *Doe 93 v. Sec’y of HHS*, ___ Fed. Cl. ___, 2011 WL 1615238, at *15-20 (Fed. Cl. April 29, 2011), *Campbell v. Sec’y of HHS*, 97 Fed. Cl. 650, 659-70 (2011) and *Rotoli v. Sec’y of HHS*, 89 Fed. Cl. 71, 82-88 (2009), *appeal docketed*, No. 10-5163 (Fed. Cir. Sept. 24, 2010), are relevant in this regard.

[Requiring a medical theory that was both reliable and persuasive] led the Special Master down a path of examining every piece of evidence relied upon by the competing experts to determine whether Petitioner had provided a persuasive medical theory that the flu vaccine likely can cause [transverse myelitis]. Imposing this burden on Petitioner was legal error. *Althen’s* Prong One merely requires a petitioner to “provide” a medical “theory” linking the vaccine to the injury. In addressing the requisite showing necessary for “providing” a medical theory linking a vaccine to an injury, courts have interpreted *Althen’s* Prong One to require a biologically plausible medical theory. *See, e.g., Andreu*, 569 F.3d at 1375 (stating that the petitioner proved causation in part because Dr. Tornatore presented a “biologically plausible” theory establishing that the vaccine can cause the injury); *Walther*, 485 F.3d at 1148 (stating that “[t]he government conceded that the Td vaccine was a biologically plausible cause of Walther’s ADEM”); *Pafford*, 451 F.3d at 1356 (discussing a special master’s finding that it was “biologically plausible” for the vaccinations at issue to cause the injury); *Campbell v. Sec’y of HHS*, No. 07–465V, at 11 (Mar. 22, 2011).

Whether a medical theory is “biologically plausible” is a far different inquiry than whether a medical theory is legally persuasive based on a preponderance of the evidence. *Althen’s* requirement that a theory linking the vaccine to the injury be biologically plausible does not mean that a petitioner must prove, as the Special Master determined, that it is more likely than not that a vaccine actually can

cause the claimed injury. Imposing this heightened evidentiary burden takes a petitioner's burden of providing a medical theory beyond the realm of biological plausibility into the realm of legal probability.

Doe 93, 2011 WL 1615238, at *16.

The special master did not find petitioners' medical evidence that Prevnar can cause intractability of seizures lacked acceptable scientific support. Rather, *Graves II* concluded that only high concentrations of Prevnar-induced IL-1 β would have that effect. The special master (1) limited the Vezzani work and Dr. Byers' citation to it; (2) limited the findings to experimental animals; and (3) justified that limitation with Hayley's clinical picture – her lack of a fever (discussed *infra*). The record contains a wealth of medical evidence of IL-1 β as a cause of seizures and their intractability. Disputes concern how much could have and did cause Hayley's seizures to become intractable and how much could have and did cause her seizures to start in the first instance. In this regard and in these circumstances, with the opinion of Hayley's treating epilepsy specialist, Dr. Wheless, discussed hereafter, that Prevnar "was associated with the onset of her seizures, which proved to be intractable and her acute encephalopathy, which then progressed to chronic encephalopathy accompanied by an intractable seizure disorder, and ultimately this was fatal and responsible for her death," petitioners' burdens were met. (Pet'rs' Ex. 43.) Furthermore, this record differs from that in the very recent case of *Cave v. Sec'y of HHS*, __ Fed. Cl. __, 2011 WL 2523438 (Fed. Cl. June 24, 2011) which respectfully declined to adopt the analysis of *Doe 93*. 2011 WL 2523438 at *25 n.18. In *Cave*, the medical theory presented was "not merely lacking in empirical support; rather it was inconsistent with available epidemiological evidence" and none of the treating physicians concluded causation between the vaccine and the injury. 2011 WL 2523438 at *16, 18.

Furthermore, the reasons for rejecting the merits of the Vezzani work and immunologist Dr. Byers' opinion embracing it among other sources, along with her experience and expertise, for her opinion that Prevnar can cause the extended duration of seizures, were inaccurate. Accordingly, Dr. Byers' expert opinion establishes the requisite causation between the Prevnar vaccination administered to Hayley and the intractability of her seizures which led to her death twenty-eight days later.

Concluding that the doses of IL-1 β causing extended seizure duration must have been much larger than represented in the published research, the special master in *Graves II* reexamined previous research by the authors of the 2008 Vezzani article titled “The Role of Cytokines in the Pathophysiology of Epilepsy,” authored by Annamaria Vezzani, Silvia Baloss and Teresa Ravizza of the Mario Negri Institute for Pharmacological Research, Department of Neuroscience in Milano, Italy, published in *Brain, Behavior, and Immunity*. Included among the seventy referenced articles are two prior works by Vezzani, et al., a 1999^{14/} and a 2000 publication. (Pet’rs’ Ex. 28 and 76, ECF No. 139-1.)^{15/}

Respondent’s expert Dr. Kohrman criticized Dr. Byers’ opinion and the underlying Vezzani research, asserting that the amounts of IL-1 β injected into the animals were “superphysiologic,” one million times what would be produced endogenously in a human. A dose that high would have catastrophic consequences to either a human or animal, resulting in a fever at minimum. (Resp’t’s Ex. O at 2-3, ECF No. 108-1.) This is the context in which the anaphylactic comment, discussed *infra*, was made. “Clinically this mega level would manifest as an acute anaphylactic reaction.” (*Id.* at 2.)

^{14/} Published in the June 15, 1999 edition of the *Journal of Neuroscience*, “Interleukin - 1 β Immunoreactivity and Microglia are Enhanced in the Rat Hippocampus by Focal Kainate Application: Functional Evidence for Enhancement of Electographic Seizures” was authored by immunopharmacologists Annamaria Vezzani, Mirko Conti, Ada De Luigi, Teresa Ravizza, Daniela Moneta, Francesco Marchesi and Maria Grazia De Simoni, members of either the Laboratory of Experimental Neurology or the Laboratory of Inflammation and Nervous System Diseases, in the Department of Neuroscience of the Istituto di Ricerche Farmacologiche “Mario Negri” in Milan, Italy.

^{15/} Published in the October 10, 2000 edition of *The Proceedings of the National Academy of Sciences*, “Powerful anticonvulsant action of IL-1 receptor antagonist on intracerebral injection and astrocytic overexpression in mice” was authored by A. Vezzani, D. Moneta, M. Conti, C. Richichi, T. Ravizza, A. De Luigi, M. G. De Simoni, G. Sperk, S. Andell-Jonsson, J. Lundkvist, K. Iverfeldt, and T. Bartfai of the Laboratories of Experimental Neurology and Inflammation and Central Nervous System Diseases, Department of Neuroscience, Mario Negri Institute for Pharmacological Research, Milano, Italy; the Department of Pharmacology, University of Innsbruck, Innsbruck, Austria; the Department of Neurochemistry and Neurotoxicology, University of Stockholm, Stockholm, Sweden; and the Harold L. Dorris Neurological Center, Department of Neuropharmacology, Scripps Research Institute, La Jolla, California. (Pet’rs’ Ex. 76, ECF No. 139-1.)

To support his opinion that mega-doses were used in the Vezzani research, Dr. Kohrman attempted to extrapolate from the concentrations of IL-1 β used on the experimental animals in the Vezzani studies to the concentration of IL-1 β in spinal fluid of young children with febrile seizures. Dr. Byers criticized this comparison and Dr. Kohrman's math: "Dr. Kohrman's calculations comparing the animal dose to humans are scientifically unsound. A quick review of the literature shows the absurdity of Dr. Kohrman's calculations." (Pet'rs' Ex. 62 at 2, ECF No. 115-2.) Dr. Kohrman later admitted that he "misread" the dosing in the Vezzani studies. (Resp't's Ex. T at 1, ECF No. 133-1.) At the February 19, 2010 hearing, there were considerable mathematical efforts to equate what ultimately was determined by the parties, and the special master, to be an apples to oranges comparison. Concentrations of IL-1 β in rat brains were simply not equivalent to concentrations in spinal fluid of seizing children with fevers. Court Trial Exhibit 1, ECF No. 135-1, is the special master's animal to human infant conversion calculations – a comparison neither party nor the special master thereafter embraced, and an animal to human link not required by the Vaccine Act.^{16/} Although Dr. Kohrman erred in his calculations and did so on several, if not all, attempts, the special master cited Dr. Kohrman's "general" opinion that more than endogenous amounts of IL-1 β would be required to prolong seizures.

Reasoning that Dr. Kohrman's math errors do not automatically validate Dr. Byers' analysis, and concluding Dr. Kohrman's general opinion that high doses of IL-1 β were used in the 2008 Vezzani research, the special master nevertheless rejected Dr. Byers' opinion. "The information provided by Dr. Byers indicates that the amount of IL-1 β given in the experiment reported in the 1999 Vezzani paper exceeded greatly the amount of IL-1 β that is produced endogenously. See Court Exhibit 1: tr. 519-22." *Graves II*, 2010 WL 5830501, at *7 (footnote omitted). The cited testimony of Dr. Byers used "close" or approximate numbers for the levels of IL-1 β found in the spinal fluid in a child of Hayley's age with a fever, with the levels of IL-1 β injected into the animals in the Vezzani experiments, after the weight/volume differentials were adjusted. Dr. Byers' mathematical assistance on this ultimately irrelevant extrapolation attempt was improperly used to discredit her

^{16/} Respondent admits "the two types of calculations (IL-1 β found in CSF of febrile children and IL-1 β injected into the hippocampus of rats and mice) could not be directly compared." (Resp't's Post-Hearing Remand Br., ECF. No. 136 at 13, n.3 (citing Tr. 496-501; 519-524, ECF No. 132).)

separate, substantive opinion that Prevnar could (and did) prolong Hayley's seizures, leading to her death.

The special master also rejected the conclusion of the 2008 Vezzani article that endogenous amounts of IL-1 β extended the seizures of experimental animals, determining that the representation in that study that the amounts were endogenous was inaccurate. "Therefore, a preponderance of the evidence shows that IL-1 β given to mice extends the duration of a seizure, which was provoked by other means, at doses that exceed the amount produced by mice normally." *Id.* at *8.

The published research was not in error. While the subject matter may appear daunting, the collective Vezzani research is fairly straightforward. The 2008 Vezzani literature concluded that the brains of experimental animals injected with IL-1 β , in concentrations determined from prior research to have been within the range of that produced naturally by the seizing brains of a prior group of experimental animals, extended the duration of the induced seizures.

The referenced 1999 Vezzani study injected one group of experimental animals with .1 ng of IL-1 β and the other with 1.0 ng. The description of these injections as "exogenous" in the 1999 work is not pertinent. The dosage, later determined to be in the range of endogenous, is. The 1999 Vezzani study concluded that .1 ng of IL-1 β did not extend seizure duration but 1.0 ng. did.^{17/} Seizures were extended in the 2000 Vezzani study with injections of 51 nanograms, an amount at least five, and as much as 50, times greater than the amounts used in the 1999 study. Dr. Byers testified that the 2000 Vezzani study also computed the range of endogenous concentrations of IL-1 β by removing the brains of a first group of seizing animals and distilling them to their respective concentration levels, and then injecting concentrations within that range into a second group of animals. Dr. Byers explained that the use of IL-1 β at the higher range of endogenous in the 2000 paper

^{17/} "The interhippocampal injection of 0.1 ng of (hr) IL1- β 10 min. before [the injection of convulsant material) was ineffective on seizure parameters, whereas 1.0 ng of (hr) IL-1 β increased by 2.3 – fold on average the time spent in kainate seizures . . . and this effect was similar to that observed after 10 ng of (hr) IL-1 β ." (Pet'rs' Ex. 28 at 7 (referring to Figure 8 on p. 9 which depicts this increase in duration graphically); see also Table 1 at 9. "Hr" refers to human recumbinant. (Pet'rs' Ex. 28 at 1.)

– 51 nanograms – may have been designed to enhance the efficacy of IL-1Ra, a suspected inhibitor/binder to IL-1 β , which was the focus of that particular study.

Recalling that the 1999 study did not address whether or not the .1 ng or 1.0 ng of IL-1 β was within the range of endogenous, from data in the 2000 Vezzani article, Dr. Byers calculated the minimum amount of IL-1 β endogenously produced by seizures: “simple calculations indicate that the smallest amount of endogenous IL-1 β which results from bicuculline induced seizures is between 1.02 and 10.2 ng.” (Pet’rs’ Ex. 77 at 2, ECF No. 139-2.) The 1.0 nanograms of exogenous IL-1 β found to prolong seizures in the 1999 Vezzani experiment falls within Dr. Byers’ results (the two hundredths of a point is determined not to be significant). The two articles are not inconsistent. Each simply used different amounts along the range of what was later determined to be endogenous concentration levels. The reasons given by the special master for rejecting the 2008 Vezzani study, which he admitted on the surface supported petitioners’ extended duration theory, were simply wrong and his conclusions in this regard were arbitrary, capricious and an abuse of discretion.

In the supplemental post-*Graves II* briefing requested by the court, respondent does not specifically embrace or defend the special master’s endogenous re-examination, but rather claims that Dr. Kahrman did not contend the Vezzani study was inaccurate as claimed by petitioners – only that the results could not be extended to humans. In the remand proceedings, Dr. Kahrman testified that his prior testimony was incorrect and that he did not mean to suggest that the animal studies presented could be relevant to Hayley’s situation.^{18/}

^{18/} Dr. Kahrman had previously testified that, while in his opinion IL-1 β does not cause seizures, it does prolong them. Discussing Exhibit 28, he testified: “It shows two things. One, that IL-1 β does not cause seizures, nor does it change the time of onset of seizure or the number of seizures, but that IL-1 β alters the time, the duration of the seizure. . . . It increased the duration of the seizure. That’s all the IL-1 β does.” (Tr. 195.) In initial proceedings, in discussing Dr. Vezzani’s work, Dr. Kahrman also testified that Prevnar could prolong seizures, referring to this adverse reaction as a “pre-prime” of the system so that “you will produce a seizure that’s longer.” (Tr. 203.) Returning to the issue presented – what doses or concentrations of IL-1 β will extend the duration of seizures, Dr. Kahrman, initially agreed. “Vezzani et al. conclude and I agree based on their data that convulsions produce the increase in Interlukin 1 beta and Interlukin 1 beta increases the convulsions in those animal[s] who are already convulsing. This paper shows that the brain must have had prior convulsions for IL-1b to have a direct effect on the convulsions.” (Resp’t’s Ex. C at 5.)

I wish to clarify my testimony during the last hearing. I at a number of points in the transcript, I said that IL-1 β increased seizures. This statement is incorrect. The only documented effect of giving IL-1 β to an animal prior to a convulsant agent is the increase in duration of the seizures in the animals, not the time to onset or the number of seizures. This is clearly documented in Vezzani exhibit 28. There is no evidence of this phenomena in humans.

(Resp't's Ex. T at 6, ECF No. 133-1; *see also* Resp't's Ex. O. ECF No. 108.)

Respondent's position on remand is not that Dr. Kohrman criticized the methodology or conclusions of the Vezzani studies; rather, respondent contends it could not be extrapolated to humans.

It should be noted that Dr. Kohrman did not attempt to re-analyze the *animal* data reported, or conclude that it was "wrong," as petitioners repeatedly claim in their supplemental brief. The researchers' findings were simply unenlightening as to the effect of IL-1 β on *human* seizures. None of Dr. Vezzani's work attempted to compare the levels of IL-1 β in rat brains following seizures to levels of IL-1 β in human brains.

(Resp't's Supp. Post Remand Br., ECF No. 145 at 13 (citation omitted).) On remand, Dr. Kohrman agreed that the Prevnar vaccine is designed to stimulate the innate immune system which results in the production of IL-1 β . (Resp't's Post-hearing Remand Br., ECF No. 132 at 15 (citing Tr. 575-76, ECF No. 132).) That the Prevnar vaccine triggers the production of IL-1 β is key to petitioners' causation theories.

Respondent contends that the medical evidence relied upon by Dr. Byers involved the direct application to the brains of the experimental animals – a delivery system that can not be extrapolated to the systemic reaction of a child to a single Prevnar vaccination. The special master also criticized the petitioners' inability to show how IL-1 β was produced in Hayley's brain – in other words, the lack of a brain biopsy was cited as a barrier to causation and compensation.

The Graveses' expert, Dr. Byers, stated that "I don't know how much IL-1beta" was produced by Hayley. When Dr. Byers was questioned further about whether any tests have been conducted to determine the amount of IL-1 β induced by Prevnar in any children, Dr. Byers indicated that these tests had been done but she could not identify any articles about Prevnar.

Dr. Byers's lack of information about how much IL-1 β a person produces in response to Prevnar leaves a gap in the Graveses' case ... Because there is no evidence that Hayley had a fever, Hayley's production of IL-1 β was less than the amount of IL-1 β needed to extend the duration of any seizure.

Graves II, 2010 WL 5830501, at *9-10 (footnotes omitted). These are criticisms of the lack of studies on humans.

The Federal Circuit has held animal studies sufficient to satisfy the burden of petitioners that a particular vaccine can cause the injury or condition suffered. The Federal Circuit dismissed the causation-defeating rationale of lack of human studies in *Andreu*:

The special master criticized [one of petitioner's doctors] for relying upon animal studies to show that the pertussis toxin can cause injury to brain tissue. *Vaccine Court Decision II*, 2008 WL 2517179 at **5-6. Quite obviously, however, scientists are unwilling to biopsy brain tissue from human infants in order to study the effects of the pertussis toxin. [That doctor] explained that "animals systems are fairly similar to one another" and that animal studies were "the best proxy" scientists have for studying brain toxicities.

569 F.3d at 1381 n.9.

The parties also dispute whether preponderant evidence was presented that the almost two-day interval from the administration of the Prevnar vaccine and the extended duration of Hayley's seizures was medically supported. Dr. Byers responded to a question as to how long the body will continue to produce IL-1 β following an immune challenge such as that presented by a Prevnar vaccination,

citing Exhibit 74, ECF No. 130-1, the Barrientos paper, that using a different agent to challenge the immune system (e. coli), rats, both young and old, had elevated levels 1, 4 and 8 days later. The Wise post-licensure Prevnar study discussed herein, states that 86.6% of the reported adverse reactions occurred within 7 days of vaccination. (Pet'rs' Ex. 21 at 2.) Drs. Byers, Kinsbourne and Wheless all agreed that the 44-hour period was appropriate. (Tr. 158, 294, 378.) The 44-hour time period from Hayley's vaccination and her intractable seizures falls within this period and the special master's conclusion that the third prong of *Althen* was not met was in error.

Contentions of the parties (*Graves I*) – causation for seizures.

Petitioners' Motion for Review filed November 13, 2008 (ECF No. 93), claims the special master in *Graves I* imposed an elevated burden of proof. Petitioners assert that they supplied all that is required under the Vaccine Act, that is a medical theory that Prevnar can cause seizures without fever supported by: (1) several medical articles and expert testimony, the credibility of which was not questioned; and (2) the conclusion of Dr. Wheless, Hayley's treating physician and renowned epilepsy expert whose reputation respondent's expert acknowledged, that (a) Prevnar can cause the onset of seizures regardless of fever; (b) Hayley's seizures, which progressed to an intractable seizure disorder and death, were caused by Prevnar; and (3) the time period between her vaccination and the onset of her seizures was medically appropriate.

Respondent defends *Graves I*, asserting that (1) the medical literature relied upon by Dr. Wheless did not establish direct causation between Prevnar and seizures without fever; (2) the small number of cases of seizures without fever following a Prevnar vaccination in the pre-licensing study relied on by Drs. Kinsbourne and Wheless was "indeterminate;" (3) contemporaneous medical records of Hayley's hospitalization did not attribute her seizures to Prevnar; (4) seizures are not uncommon in children and sometimes causes are simply not found; and (5) the biological theories of how the Prevnar vaccine could and did cause Hayley's seizures were based on animal, not human experiments.

Dr. Byers's entire theory that Prevnar vaccine could initiate an innate immune response causing de novo afebrile seizures is based on animal models and their production of, and response to, IL-1 β . Dr. Byers's

piecemeal use of the articles and her attempts to extrapolate their results to humans were not persuasive to the Special Master, and his finding that her opinion was unreliable is well-supported in his decision.

(Resp't's Resp. to Mot. for Review, ECF No. 95 at 29 (citations omitted).)

While contending a biological mechanism or theory of how the Prevnar vaccine could and did cause seizures is not required, petitioners assert nevertheless, immunologist Dr. Byers provided such and the special master's rejection of petitioners' causation theories because of a dearth of human animal studies, was erroneous.

Data on human studies was submitted. Dr. Kinsbourne addressed two medical articles documenting that minor infections in humans can precipitate seizures without fever depending upon the seizure threshold of the individual.^{19/} Dr. Kinsbourne testified that the immunological challenges were akin to those with vaccinations and supported Dr. Byers' opinion. (Tr. 372-77.)

Dr. Byers testified as to the biological mechanism of how a Prevnar vaccine can cause seizures and relied on numerous medical articles in support. In sum, Dr. Byers explained that in creating desired immunity, cytokine releases can produce fever, seizures or both. (Tr. 321-33, 105-07, 121-23.)

Dr. Wheless' explanation was similar.

^{19/} Published in 2005 in Volume 46 of *Epilepsia*, "Nonfebrile illness seizures; a unique seizure category?" was authored by Danielle M. Zerr, Heidi K. Blume, Anne T. Berg, Mark A. Del Beccaro, Sidney M. Gospe, Jr., Amanda L. Allpress, and Dimitri A. Christakis of the Department of Pediatrics and Neurology, University of Washington and Childrens Hospital and Regional Medical Center, Seattle, Washington; and Neuroepidemiology Group, NIU/BIOS, DeKalb, Illinois. (Pet'rs' Ex. 51.)

Published in 2004 in Volume 31 of *Pediatric Neurology*, "Afebrile seizures associated with minor infections: comparison with febrile seizures and unprovoked seizures" was authored by Wei-Ling Lee, MD and Hian-Tat Ong, MD of the National Neuroscience Institute and Department of Pediatrics, National University of Singapore, Singapore. (Pet'rs' Ex. 52.)

A: Okay. Well, the vaccine, as you know, just like any vaccine, it's given locally, but it has to become systemic or there will be no point in vaccinating anyone because it has to become systemic to work. It has to get into the blood system. It has to be distributed throughout the body to do what it's supposed to do as far as keeping someone from getting the illness.

When it does that, the goal is for the vaccine to stimulate the person's immune system, and if all goes well, to stimulate the immune system in a way that if they're ever exposed to that infectious agent that they will react to it.

As you're aware, unfortunately some of the time when the vaccine stimulates the immune system, which is its intended goal, it attacks the nervous system. It can be either the central nervous system or the peripheral nervous system.

So if it's the peripheral, we have well documented cases of people with Guillain-Barre or other problems outside of the brain that are spinal cord or peripheral nerve. If the immune attack involves the brain, we can have seizures with it. So it's part of the mechanism we hope for for the vaccine. It has to stimulate receptors to normally work. We now know very well that those same receptors are actually found on the surface of the brain, and, for example, those same receptors are involved in the genesis of seizures with fever also. So we know that those are there.

(Tr. 297- 98.)

The special master concluded that petitioners failed to provide preponderant evidence that Prevnar could, and did, cause the onset of seizures in nine-month-old Hayley in the absence of fever or other less-than-seizure reaction. Indeed, the record is replete with spirited, highly technical disagreement among medical specialists about whether or not a fever is a required precursor to Prevnar-induced seizures. The special master did not find that the Prevnar vaccine did not cause seizures, only a fever or other lesser response would manifest first. The absence of a fever was a bright-line predicate.

Hayley was healthy for the first 44 hours after vaccination. If Dr. Byers's theory that she was producing so much IL-1 β that eventually

the IL-1 β caused a seizure were correct, then there would probably be an intermediate sign of an adverse reaction. For example, Hayley may have had a local reaction (such as swelling or redness on her arm) or she may have had a fever. But, she did not.

Graves I, 2008 WL 4763730, at *16. The special master discounted the expert opinions of Drs. Byers and Kinsbourne and treating physician specialist Dr. Wheless that the Prevnar vaccine could and did cause Hayley's seizures regardless of whether or not she had a fever.

The two neurologists retained by the Graveses believe that Prevnar can cause seizures in the absence of fever. Dr. Kinsbourne and Dr. Wheless base their opinion, at least in part, on the Wise article and the entry for Prevnar in the Physicians' Desk Reference (PDR). These articles, however, do not show that Prevnar causes seizures in the absence of fever.

The Graveses also presented the testimony of Dr. Byers, who also believes that Prevnar can cause seizures without a fever. Dr. Byers's opinion is also not persuasive.

Graves I, 2008 WL 4763730, at *5.

In rejecting these causation opinions, the special master cited what he described as the consistent general trend and accumulated knowledge of the special masters that fevers accompany vaccine-induced seizures.

The proposition that a fever causes seizures is well-accepted. See tr. 133-34 (Dr. Byers); *Adams v. Sec'y of Health & Human Servs.*, 76 Fed. Cl. 23, 25 n.6 (2007) (citing 1994 report from Institute of Medicine and finding that petitioner established that Prevnar caused febrile seizures leading to epilepsy); *Terran v. Sec'y of Health & Human Servs.*, No. 95-451V, 1998 WL 55290 (Fed. Cl. Spec. Mstr. Jan. 23, 1998), *aff'd*, 41 Fed. Cl. 330 (1998), *aff'd*, 195 F.3d 1302 (Fed. Cir. 1999). In some cases, a vaccine can produce a fever that leads to a seizure. In these cases, the vaccine causes a "febrile seizure."

In contrast, seizures that are not associated with fevers are called “afebrile seizures.” Cases in the Vaccine Program have consistently found that a vaccine is not the cause of a seizure that happens in absence of a fever. *E.g.*, *Andreu ex rel. Andreu v. Sec’y of Health & Human Servs.*, No. 99-817V, 2008 WL 3842915 *3 (Fed. Cl. July 23, 2008) (sustaining decision of special master denying compensation); *Valico v. Sec’y of Health & Human Servs.*, No. 00-662V, 2002 WL 508344 *4 (Fed. Cl. Spec. Mstr. Mar. 11, 2002) (DTaP). The only exception appears to be *Almeida v. Sec’y of Health & Human Servs.*, No. 96-412V, 1999 WL 1277566 (Fed. Cl. Spec. Mstr. Dec. 20, 1999) (DTaP). Thus, the general trend in the Office of Special Masters has been to recognize that vaccines may cause seizures with fever, but also to recognize, with one exception, that vaccines do not cause seizures without fever. *See Althen*, 418 F.3d at 1281 (quoting *Hodges v. Sec’y of Health & Human Servs.*, 9 F.3d 958, 961 (Fed. Cir. 1993) and permitting special masters to use their “accumulated expertise” to decide cases).

Graves I, 2008 WL 4763730, at *9.

Subsequently, the opinion in *Andreu* cited by the special master, was reversed by the Federal Circuit on this point, finding the special master erred in rejecting the opinion of petitioners’ treating physician. Petitioners had alleged that their son’s receipt of the diphtheria-pertussis-tetanus (“DPT”) vaccine caused his seizure disorder, and offered a biologically plausible, though unproven theory of causation, which hypothesized that the pertussis contained within the vaccine could cross the blood-brain barrier to induce seizures. 569 F.3d at 1371. In support, the expert provided research that observed this mechanism in animals. *Id.* The child’s treating physicians also testified to their opinion that the child’s condition was caused by the vaccination. *Id.* at 1372-73. Respondent’s expert did not dispute the plausibility of the blood-brain barrier theory, but similar to the opinions expressed in the instant case, opined that the theory was inapplicable because of the child’s clinical picture – specifically the child did not have a fever. *Id.* at 1372. Concluding the special master through the guise of expert reliability/credibility and exercise of discretion, improperly elevated petitioners’ burden of proof, the Federal Circuit concluded that *Althen* prong one – a “biologically plausible’ theory” of causation was met. *Id.* at 1375. Continuing as pertinent here, the Federal Circuit reaffirmed that

circumstantial evidence and statements of treating physicians may support causation, with the court ultimately concluding that petitioners also met their burden of proving causation-in-fact, *Althen*'s second prong. *Id.* at 1375-83.

In *Graves I* the special master required the same predicate fever. As in *Andreu*, using a fever to determine outcome was error. As in *Andreu*, Dr. Wheless, Hayley's treating physician, opined as to causation and there was no disagreement over whether the vaccine could cause seizures. 569 F.3d at 1378.^{20/}

^{20/} Subsequently, in *Moberly v. Sec'y of HHS*, 592 F.3d 1315 (Fed. Cir. 2010) the Federal Circuit affirmed the denial of compensation. In *Moberly*, none of the treating physicians opined that the vaccination caused the injury. Rather, the record evidence supporting the opinion of the petitioner's expert "amount[ed] at most to a showing of temporal association between a vaccination and a seizure, together with the absence of any other identified cause for the . . . injury." *Id.* at 1323. The *Moberly* panel differentiated *Andreu*.

In *Andreu*, however, there was direct testimony from *Andreu*'s treating physicians stating "unequivocally" that the DPT inoculation caused his seizures. 569 F.3d at 1376. While testimony from treating physicians is not required in Vaccine Act cases, it can provide supporting evidence of causation, and it did so in *Andreu*. In this case, by contrast, there was no treating physician evidence that supported the claim of causation. To the contrary, to the extent the treating physician evidence bore on causation, it was negative, as the principal treating physician, Dr. Torkelson, expressed skepticism that Molly's condition was caused by her DPT vaccination.

Furthermore, in *Andreu* this court held that the "blood-brain barrier" theory should have been credited because the government's expert witness did not dispute the biological plausibility of the theory and thus failed to cast it into doubt. 569 F.3d at 1377. In this case, by contrast, the government's expert witness did not concede the biological plausibility of the "blood-brain barrier" theory, and in fact testified that "people in the field don't think it's biologically plausible." Moreover, the petitioners' expert witness undercut his own position by conceding not only that the blood-brain barrier theory had never been tested, but also that there was no evidence suggesting that it applied to Molly's case. Because the evidentiary record in the *Andreu* case is significantly different from the record in this case, the result in *Andreu* does not compel the same result here.

592 F.3d at 1325.

In *Liable v. Sec’y of HHS*, 2000 WL 1517672 (2000), cited by the special master as another exception to the perceived dearth of compensation for vaccine-caused seizures without a fever, the special master noted that the experts did not focus on whether the seizures were accompanied by fever, concluding that regardless of whether there was a fever at the time of the initial seizure, causation was established. *Id.* at *13. See also *Almeida v. Sec’y of HHS*, 1999 WL 1277566, at *1 (Fed. Cl. Spec. Mstr. Dec. 20, 1999) (finding causation where the petitioner had a seizure without a fever on the evening she received a DPaT vaccination and her “doctors ordered the elimination of the pertussis component from future shots.”).^{21/}

Another special master recently declined to view fever as a gatekeeper to compensation. *Romero v. Sec’y of HHS*, 2010 WL 2766761, at *12-16 (Fed. Cl. Spec. Mstr. June 22, 2010) (citing *Andreu* and *Moberly*, finding causation between DPaT vaccine and seizures, either with or without a fever, even without a treating physician opinion on causation or consensus on biological mechanism).

Special masters are not bound by decisions of other special masters. *Hanlon v. Sec’y HHS*, 40 Fed. Cl. 625, 630 (1998), *aff’d*, 191 F.3d 1344 (Fed. Cir. 1999) (“Special masters are neither bound by their own decisions nor by cases from the Court of Federal Claims, except, of course, in the same case on remand.”). Nevertheless, recent decisions, particularly *Andreu*, that did not endorse the fever/no fever brightline, suggest that any “general trend” or “accumulated expertise” cited by the special master, no longer supports the denial of compensation in *Graves I* as there articulated.

Moreover, as in the *Graves II* remand decision, in this area bereft of medical proof, the special master’s requirement that petitioners provide preponderant evidence of a biological theory of how the Prevnar vaccine can cause the instigation of seizures without fever in addition to expert medical testimony that it could, raised the evidence bar too high. *Althen*, 418 F.3d at 1280. In addressing the medical theories of how the Prevnar vaccine induces the production of the cytokine IL-1 β which in turn, activates or causes firing inside the brain, instead of addressing a

^{21/} In *Andreu* the Federal Circuit cited *Almeida* with favor four times: 569 F.3d at 1377, 1378, and 1382 (twice), and *Liable* six times: 569 F.3d at 1374, 1375 n.1, 1376, 1378 n.6, 1380 and 1382. See *Romero v. Sec’y of HHS*, 2010 WL 2766761, at *12 (Fed. Cl. Spec. Mstr. June 22, 2010).

“plausible” medical theory, the special master required preponderant substantive evidence, akin to scientific acceptance.

Also as noted in discussing *Graves II*, recent decisions applying the Vaccine Act hold that reliable, biologically plausible theories that a vaccine could cause the injuries suffered satisfied or complied with *Althen* prong one. *Doe 93 v. Sec’y of HHS*, ___ Fed. Cl. ___, 2011 WL 1615238, at *15-22 (Fed. Cl. April 29, 2011) (subjecting a medical theory that the vaccine can cause the injury complained to a preponderant evidence review, improperly elevated petitioner’s burden, citing *Andreu*, *Walther*, and *Pafford*); *Campbell v. Sec’y of HHS*, 97 Fed. Cl. 650 (2011) (concluding criticism of the medical theories on how the vaccine could cause the injuries as a practical matter required near scientific certainty); *Rotoli v. Sec’y of HHS*, 89 Fed. Cl. 71, 82-88 (2009) (finding petitioners provided reliable medical theory that the vaccine could cause the injury and that the special master erroneously applied his assessment of the credibility of petitioners’ medical experts, contrary to *Andreu*); *Doe 21 v. Sec’y of HHS*, 88 Fed. Cl. 178, 199 (2009) (finding petitioner provided a biologically plausible theory of causation between the vaccine and the injury suffered).

The court concludes, under the circumstances here, that the rejection of the accepted medical theories of causation between the Prevnar vaccine and seizures absent a fever was unwarranted under fact and law. First, to reiterate, as *Andreu* instructed, the existence of a fever as a talisman to causation can be error. Even if a fever is required for the biological plausibility of medical theories presented, the record evidence is not clear that Hayley did not have a fever condition during relevant times, particularly when her seizures were continuous and fever-reducing medications were repeatedly given. The affidavit of Hayley’s mother, Lisa Graves, states that Hayley was restless and stayed awake later than usual on August 9, 2000, the day after her vaccination, and on the following morning “did not appear right. The left side of her body was moving and it would not stop.” (Pet., Lisa Graves’ Aff. at 2.) Medical records document crying, fussiness and the administration of Motrin, ibuprofen and other medications which, although perhaps given for

discomfort, are fever reducers.^{22/} Secondly, fussiness or irritability, other less-than-seizure fever precursors are prevalent in the record.^{23/}

Also, as occurred in *Andreu*, with respect to the opinion of the treating physicians, the special master here erred in his treatment of the opinion of Dr. James Wheless, Hayley's treating pediatric neurologist. Dr. Wheless^{24/} was Hayley's treating pediatric neurologist following her transfer from Cook Hospital to Hermann

^{22/} Ibuprofen, including the brand name Motrin, and acetaminophen, including Tylenol, are fever reducers. *Physicians' Desk Reference* (65th ed. 2011) 1902-03, 1908-09.

Neither party placed particular significance on the administration of fever-reducing medications when questioned by the court at oral argument.

^{23/} In this regard, the special master commented on notes in Hayley's medical records that she drank four ounces (a half a cup) of formula on the morning her seizing commenced, suggesting she had no effects from the vaccination. In the circumstances presented, it would be arbitrary and capricious, and an abuse of discretion, should this isolated notation trump other references in the record of possible adverse reactions (elevated temperature, fussiness and crying), if objective physical manifestations prior to the onset of seizures are required to embrace the confines of the medical research and theories.

^{24/} At the time of his December 14, 2007 opinion (Pet'rs' Ex. 43), Dr. Wheless was a professor and Chief of Pediatric Neurology at the University of Tennessee College of Medicine, Health Science Center, in Memphis, Tennessee. He also was a director of both the Comprehensive Epilepsy Program and the Neuroscience Center, at the Le Bonheur Children's Medical Center. He was the Clinical Director and Chief of Pediatric Neurology at St. Jude Children's Research Hospital, all in Memphis, positions he had held for some two years. For five years prior to that time, he was professor of Neurology and Pediatrics at the University of Texas Health Science Center at Houston, Texas; and Director, Epilepsy/EEG Fellowship Program; Director, Pediatric Epilepsy Services; Director, Epilepsy Monitoring Unit; Director, Texas Comprehensive Epilepsy Program; and Head, Clinical Neurophysiology – Memorial Hermann/Children's Memorial Hermann Hospital in Houston, Texas. This is where and when Hayley was hospitalized.

Prior to those positions, Dr. Wheless was an associate professor of Neurology and Pediatrics at the University of Tennessee College of Medicine, and the Medical Director of the Epilepsy Monitoring Unit and Medical Director and co-founder of the Texas Comprehensive Epilepsy Program, also in Houston.

Dr. Wheless is board certified in pediatrics, pediatrics and psychiatry with special competence in pediatric neurology and clinical neurophysiology. His extensive publications, certifications, memberships and offices held in professional organizations, education and honors, are contained in his Curriculum Vitae. (Pet'rs' Ex. 44.)

– a transfer with his consent, specifically so she could be placed in his care. Dr. Wheless testified in this proceeding that he believed Pevnar caused the onset of Hayley’s seizures, and he believed this at the time he was treating her. Nevertheless, the special master did not accord special credence to his opinion because (1) Dr. Wheless was paid for his time; and (2) he did not contemporaneously record this causation opinion in Hayley’s treatment notes.

Dr. Wheless’ causation opinion relates back to the time Hayley was his patient in 2002. To discount or reject Dr. Wheless’ expert causation opinion because it was not recorded contemporaneously in medical records, or because he was subsequently compensated for his expert testimony, was erroneous, arbitrary, and capricious. Dr. Wheless was Hayley’s treating physician and his expert opinion had its genesis in his medical experience with her treatment and the medical literature he studied. The special master partially retracted one basis for his rejection of Dr. Wheless’ opinion in a footnote, stating he was not suggesting that compensation influenced Dr. Wheless.^{25/}

Respondent’s expert, Dr. Kohrman, testified he considered Dr. Wheless to be “a very good pediatric epileptologist.”^{26/} (Tr. 242.) Dr. Wheless testified in this proceeding that the 2004 Wise post-licensure study published in JAMA subsequent to his treatment of Hayley, together with other medical articles, the PDR and Medimedex, confirmed and further supported his causation opinion. Besides the medical literature he cited in support at several hearings, discussed hereinafter, Dr.

^{25/} The text should not be interpreted to suggest, in any way, that compensation influenced Dr. Wheless’s opinion. Dr. Wheless appeared sincere in his testimony in the sense that he honestly believed the opinion he was expressing. However, sincerity and honesty are not the measure of an expert. The expert must persuade that his opinion is more likely than not true. Dr. Kinsbourne and Dr. Kohrman, who hold opposite opinions, also appeared honest and sincere.

Graves I, 2008 WL 4763730, at 17 n.2.

Presumably, all medical experts, including respondent’s, were compensated.

^{26/} An epileptologist is a neurologist who specializes in the treatment of epilepsy. *Dorland’s Illustrated Medical Dictionary* (31st ed. 2007) at 641.

Wheless was also informed by his experience and his intensive treatment of this child.

Dr. Wheless' testimony and opinion that the Prevnar vaccine administered to Hayley on August 8, 2000, caused the onset of her seizures less than two days later, became intractable and led to her death, touches on all three *Althen* prongs – that Prevnar can cause seizures without fever; that Prevnar did cause seizures in Hayley regardless of whether she had a fever; and that the forty-four hour time period from vaccination to first seizure was within medical parameters. *Capizzano v. Sec'y of HHS*, 440 F.3d 1317, 1326 (Fed. Cir. 2006) (“We see no reason why evidence used to satisfy one of the *Althen III* prongs cannot overlap to satisfy another prong.”).

A rule that a treating physician's opinion evidence based on that treating experience, must be discounted if compensated would eviscerate the favorable status accorded such evidence in contravention of the Federal Circuit's instruction in *Andreu* that “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.” 569 F.3d at 1375 (quoting *Capizzano*, 440 F.3d at 1326). *See also Broekelschen*, 618 F.3d at 1347.

In the fervor of attempting to save Hayley's life, it is unreasonable to require a treating physician to scribe legal conclusions in his or her treatment notes as the court in *Doe 93* observed:

Any expectation that treating physicians will record the precise biological theories behind their belief that a patient's condition was caused by a particular trigger is discordant with the reality of medical treatment. Doctors are and must be concerned with treating patients, not with articulating the precise biological theories upon which they base their diagnoses.

2011 WL 1615238, at *22 (quoting *Campbell v. Sec'y of HHS*, 97 Fed. Cl. 650, 671 (2011)).

Treating doctors rarely, if ever, provide medical theories of causation; they do provide critical circumstantial evidence. . . . [T]reating physicians rarely discuss ‘theories’ in their notations. Theories are not

relevant to the clinician's agenda, which is to identify, treat, and heal. If treating physicians needed to list their 'theories' before their opinions became probative in the Vaccine Program, then no medical record would be probative. Clinicians simply don't have the time to indulge in theorizing.

Carter v. Sec'y of HHS, 2007 WL 415185, at *21 n.25 (Fed. Cl. Spec. Mstr. Jan. 19, 2007) (quoting *Capizzano*, Ruling on Remand, 2006 WL 3419789 (Fed. Cl. Spec. Mstr. Nov. 8, 2006)).

At the time Dr. Wheless was treating Hayley, Prevnar was a newly-licensed vaccine. While there had been pre-licensing testing, medical venting of adverse effects was limited. Nevertheless, Dr. Wheless testified that at the time he was treating Hayley, he believed that her Prevnar vaccination caused her seizures. While he did not contemporaneously record that opinion in her medical records, there are references in that record that corroborate that opinion. A vaccine reaction is included in differential diagnoses as are questions of whether Hayley's condition was vaccine-related and phone calls to the manufacturer.^{27/} Differential diagnoses by others that include vaccine causation is further confirmation of a logical cause and effect. See *Campbell*, 97 Fed. Cl. at 671 n.45 (“The fact that the vaccine was considered a possible cause shows that from the treaters' vantage point, the clinical

^{27/} The August 18, 2000 differential diagnoses of an infectious disease consulting physician at Cook Hospital included “vaccine reaction;” recommendations included contacting the manufacturer. (Pet'rs' Ex. 9 at 61.) August 19 and 21 entries included “[a]waiting phone call from Prevnar manufacturer next week but doubt this is the source - will follow[s],” and “[w]ill speak [with] manufacturer of Prevnar today if he calls.” (*Id.* at 64, 69.) Entries for August 22, 23 and 24 contained “[manufacturer] still to call us – not done yet. Mary Jackson coordinating;” “Mary Jackson spoke [with vaccine manufacturer] – they are searching their database, and will send their findings and an adverse event report form within 2 weeks;” and “[Patient] is reported to [manufacturer] for potential adverse [reaction] to Prevnar. . . .” (*Id.* at 71, 73 and 74.) Possible vaccine reaction was included in consultation notes of Dr. Suzanne Whitworth dated August 18, 2000. (*Id.* at 108.)

Pediatric neurology consultation notes from Hermann Hospital dated September 14 include “will discuss [with] Dr. Wheless – possible vaccine related CNS [central nervous system] syndrome may need to be considered.” (Pet'rs' Ex. 3 at 84.) Another consulting physician wrote on September 2: “poss[ible] post-vaccination reaction.” (Pet'rs' Ex. 10 at 313.)

sequence was logical.” (quoting *Capizzano v. Sec’y of HHS*, 2006 WL 3419789, at *14 (Fed. Cl. Spec. Mstr. Nov. 8, 2006).)

Nevertheless, an undisputed confirmation of Dr. Wheless’ opinion, or at minimum suspicion, of causation at that time was his 2000 referral of petitioners to Mr. Gage, their counsel in this matter, with whom Dr. Wheless was familiar based on one previous referral of an adverse vaccine reaction.

Q. Okay. Did you [at the time he was Hayley’s treating physician] . . . did you suspect the vaccination, the Prevnar vaccination, as the potential cause of Hayley’s seizures?

A. At that time, yes, it was suspected as a potential cause.

Q. And will you just tell the Special Master if you know how it was that the Graves came to call me as an attorney to file a petition for them?

A. Yes, I referred the Graves to your office both because of my concern that the vaccine was the cause and then as subsequent data has come out confirming that as a possible cause, but at the time, it was because of my feeling that that was the cause of her death.

Q. Okay. And your opinion now, obviously its been eight years since you were her doctor, you treated her, what is your opinion now as an epileptologist and looking back on your treatment of her as to what the cause of her seizures was?

A. I think my opinion is still the same. I think there was the vaccination. I think subsequent studies have confirmed that, which they often do in postmarketing studies. There’s a limited exposure of children to whether it’s a vaccine or the drug prior exposure, prior to widespread release, we gain a lot more information after the drug’s widely used, that that’s the purpose of the FDA having an active Phase 4 surveillance program is to pick up things like this that we know are rare and unlikely to be picked up during the regular trials.

Q. And when you’re talking about postlicensure work, are you referring to the Weiss [sic] article?

A. Yes.

Q. Postlicensure study.

A. Yes.

(Tr. 272-74.)

Furthermore, during the period of Hayley’s treatment, substantial efforts were made to rule out other potential causes. There were consultations with numerous specialists, testing and alternate treatment, none of which was successful. While petitioners are not required to rule out other possible causes of Hayley’s seizures, eliminating alternatives can bolster causation. *Walther v. Sec’y of HHS*, 485 F.3d 1146, 1149-50 (Fed. Cir. 2007). Setting aside the special master’s comment that Hayley’s condition was likely caused by biotendase deficiency – a possible alternative discarded by respondent and its experts, the special master did not credit this diagnostic investigation and elimination.

Giving appropriate credit to the opinion of Dr. Wheless, the treating pediatric neurologist, and given the absence of any other reason for the sudden onset of Hayley’s intractable seizures which, despite her continuous specialized hospitalization, litany of tests and treatments and examination by specialists did not stop, the preponderant credible evidence bar of causation was met.

In *Graves II*, the special master added to his rationale for not accepting the conclusions of Dr. Wheless, perceived limitations in the medical literature Dr. Wheless cited for support. The medical sources relied upon by Dr. Wheless and the special master’s comments thereon include:

A. The Physicians’ Desk Reference (“PDR”). (Pet’rs’ Ex. 19.)

The PDR (2003 edition) reported adverse reactions from Prevnar, a then-relatively new vaccine, in pre-licensure studies on a relatively small population of several thousand subjects. From that group, eight individuals receiving a Prevnar vaccination reported seizures compared with four in the control group. Although statistically small, that Prevnar doubled the seizure rate was significant, particularly since the control group was not given a placebo, but another vaccine itself prone to cause seizures. Accordingly, a 100% increase in seizure rate over a group given another vaccine known to cause seizures, was significant. *Stapleford v. Sec’y of HHS*, 2009 WL 1456441, at *9-11 (May 1, 2009), *aff’d*, 89 Fed. Cl. 456 (2009) (collecting vaccine cases relying at least in part on the PDR, some successfully, some not, recognizing that the PDR may be circumstantial evidence of causation).

B. The Micromedex article. (Pet’rs’ Ex. 20.)

Micromedex is a healthcare research engine that provides drug summaries for doctors and tools for healthcare professionals. Online access to the system is

available through a purchased license service akin to Westlaw and LEXIS legal research services. See *Joeckel v. Principi*, 2001 WL 669834, at *1 (Vet. App. 2001). Micromedex warned of adverse side effects of Prevnar including seizures, again without categorizing as with or without a fever. Fever, defined as temperature over 39 degrees Celsius, was separately listed as an adverse reaction.

C. The Wise post-licensure study. (Pet’rs’ Ex. 21.)

The Wise post-licensure article is a peer-reviewed study of adverse effects of the Prevnar vaccine that was published in the *Journal of the American Medical Association* (“JAMA”) in 2004. The authors explained that one of the reasons that this Phase 4 post-licensure study^{28/} was undertaken was the increased seizure rate in the prelicensure study referenced in the PDR.

In the primary clinical trial before licensure, a few more patients had seizures within 3 days after [Prevnar] than after the meningococcal comparator vaccine^{29/} (8 vs[.] 4), raising concern about a possible association.

(Pet’rs’ Ex. 21 at 7 (footnote added).)

This study analyzed the Vaccine Adverse Events Reporting System (“VAERS”) of the Prevnar vaccine over a two-year period, consisting of 4,154 voluntarily-self-submitted reports of harmful or contrary effects experienced following vaccination. Reported events included 393 seizures of which 299 were without a fever.^{30/} Symptoms began within one week of the vaccination in 86

^{28/} Phase 4 studies “delineate additional information about the drug’s risks, benefits, and optimal use.” 21 C.F.R. 312.85 (2004).

^{29/} Again, this “control” vaccine caused seizures, lending to the increased concern about Prevnar which had twice as many seizures.

^{30/} Jointly operated by the FDA and the Centers for Disease Control and Prevention (CDC) since 1990, VAERS accepts voluntarily submitted reports of events from manufacturers, health care workers, and patients. . . . Reported events may be a small fraction of all that occur, and they frequently defy facile assessment of whether vaccinations played a causal role. Nonetheless, the potential to detect

percent of the cases and included 117 deaths. Three deaths were reported from seizures without evident etiologies, one being Hayley.^{31/} A pair of fraternal twins suffered an initial onset of seizures after administration of the vaccine, reactions Dr. Kinsbourne opined was very unlikely to be coincidental.^{32/}

Also, two incidents of seizures in a positive rechallenge were reported; that is after an initial unprovoked Prevnar seizure, the vaccine was repeated (the rechallenge) and the seizures occurred again – which petitioners’ experts testified

important clues from patterns among collected reports warrants careful surveillance.

(Pet’rs’ Ex. 21 at 2.)

^{31/} “Three patients who died had seizures without evident etiologies. A 9-month-old female developed status epilepticus 2 days after her second dose of [Prevnar]” (Pet’rs’ Ex. 21 at 4-5.)

^{32/} Dr. Kinsbourne testified:

Q Okay. Would you explain to the Special Master what significance there is to a pair of fraternal twins having seizure onset after receipt of this vaccine?

A Well, to have two children, both have seizures after a particular immunization, it raises the question of some predisposition that those children might have had, towards reacting in that way towards a vaccine, towards which millions don't react with seizures. There is something special in the genomes.

Now the fraternal twins, they are not identical, which means that they shared only 50 percent of the genetic inheritance from their parents. But presumably the, what I call susceptibility factor, the genetic susceptibility factor was within that section of their genomes.

The argument that the seizure disorder began coincidentally after the vaccination is very weak. If both the twins react in that same very unusual way to a given vaccine given at the same time, presumably the same doctor.

Q Can you, how likely is it, Doctor, that two fraternal twins are just simply going to, by chance, develop seizures at the same time?

...

THE WITNESS: I think I have enough background to say that it’s very, very unlikely.

(Tr. 41-42.)

was strong evidence of causation. Indeed, this special master previously granted compensation in another case, citing the petitioner's adverse effects from a first vaccination and worsening effects from the second. See *Hall v. Sec'y of HHS*, 2007 WL 3120284, at *7 (Fed. Cl. Spec. Mstr. Oct. 4, 2007) (“A rechallenge event occurs when a patient who had an adverse reaction to a vaccine suffers worsened symptoms after an additional injection of the vaccine.” (citing *Capizzano*, 440 F.3d at 1322)).

Admittedly, the United States Court of Federal Claims “uniformly has upheld the . . . concerns about the reliability of VAERS data.” *Analla v. Sec'y of HHS*, 70 Fed. Cl. 552, 558 (2006) (citing cases). However, here, raw VAERS data was not offered. Dr. Wise's study used the data as a base and delved deeper into the adverse consequences there reported. It was also one of several sources relied upon by Hayley's treating specialist, and under the circumstances presented, appropriately included in attaining and exceeding the preponderant evidence bar, or at minimum the inclusion of this report among the other literature cited did not, by association, require wholesale rejection of the resulting opinions.

Rather than crediting the opinions of Drs. Wheless, Byers and Kinsbourne, the special master adopted Dr. Kohrman's comparison of the percentage of reported seizures without fever per doses in the Wise post-licensure study to the rate of seizures without fever in the general infant population reported in the Camfield literature (Resp't's Ex. N)^{33/} and concluded that the incidence of reported seizures without fever following a Prevnar vaccination did not exceed the rate of seizures without fever in the general infant population. “Approximately two seizures per million doses is very close to the overall expected rate of seizures during the first year of life in general. . . . [T]hus, an analysis of the numbers from the Wise article does not indicate that Prevnar caused any seizures.” *Graves I*, 2008 WL 4763730, at *7.

Petitioners further claim that the admittedly limited self-reporting in the VAERS database, compared with actual data of the infant seizure rate was erroneous. The court agrees the statistical analysis was flawed. Consequently, the rationale for concluding in *Graves I* that the opinions of Drs. Byers and Kinsbourne

^{33/} Peter R. Camfield and Carol S. Camfield, “Pediatric Epilepsy: An Overview,” *Pediatric Neurology, Principles & Practice* (3rd ed.) 629, 631.

and, in *Graves II*, the opinion of treating physician Dr. Wheless, that the Prevnar vaccine could and did cause Hayley's seizures were not reliable, because they relied in part on the Wise study, was erroneous, arbitrary and capricious and an abuse of discretion.

Of the 393 seizures following a Prevnar vaccine reported in VAERS, 299 cases (more than 76%) were not accompanied by a fever. The authors of the Wise report arbitrarily took ninety-eight of those 393 to determine if those individuals had a prior history of seizures. Respondent does not claim the ninety-eight was a random sampling.^{34/} Of that group, nineteen – 19.4 % did not have a fever with the initial post-Prevnar seizure. (Pet'rs' Ex. 21 at 1, 2 and 5.) Extrapolating 19.4 % to the number of doses of Prevnar "distributed," Dr. Kohrman concluded a rate of 2.6 incidents of unprovoked seizures per 1,000,000 doses of Prevnar. Dr. Kohrman concluded that rate was similar to the rate of seizures in infants up to one year old obtained from the Camfield report, 110 per 100,000 children, or approximately 3 per 1,000,000 children per year. (Tr. 185.)^{35/} The special master accepted Dr. Kohrman's conclusion "that the Wise article does not show a higher rate of seizures without fever after Prevnar," as persuasive. *Graves I*, 2008 WL 4763730, at *7-8.

^{34/}

THE COURT: Right. What I guess I want to be clear is that the reduction from 393 convulsions, the broad category, to 98 cases that were studied in detail, were just because those are the first 98 cases that walked through the door.

[Dr. Kohrman]: Yes, it was just, it was those chance cases that they got the extra information on.

(Tr. 217.)

^{35/} The incidence of unprovoked seizures is the highest in the first year of life.

The overall incidence of childhood epilepsy from birth to 16 years is approximately 40 in 100,000 children per year. The incidence in the first year of life is about 120 in 100,000. Between 1 and 10 years of age, the incidence plateaus at 40 to 50 in 100,000 and then drops further in the teenage years to about 20 in 100,000.

(Resp't's Ex. N at 629 (internal citations omitted).)

Instead of the ratio of seizures without fever to total seizures in the Wise post-licensure study being 19/98, petitioners assert the denominator should have been 300 – the total number of seizures out of the total of 4,154 adverse events reported, resulting in a fifteen-fold increase in the unprovoked seizures of the Prevnar groups represented in the VAERS study. Petitioners also cite to the special master’s recognition that VAERS reports underlying the Wise analysis are voluntarily submitted and under-reported, meaning the actual number of seizures without fever are larger, further eroding the special master’s conclusion that the rate of unprovoked seizures does not exceed the background rate in the general population. (Pet’rs’ Mot. for Review, ECF No. 93 at 15-19.)

Respondent defends the use of the subset of ninety-eight. “The authors of the Wise article – not the Special Master or Dr. Kohrman – selected a subset of ninety-eight cases of seizures reported after the vaccination for examination.” (Resp’t’s Resp. Mot. Rev., ECF No. 95 at 27.)

The VAERS data on which the Wise article was based, was not segregated by age, nor was it segregated by year. The Camfield data was presented by year and by age groups.^{36/} The Camfield rate of unprovoked seizures for infants is higher than any other age category (40 per 100,000 from birth to age 16, versus 120 per 100,000 in the first year of life). Use of the seizure incident rate in infants artificially elevates the so-called background rate, making a comparison to a seizure incidence rate following a Prevnar vaccination less of a contrast. A conclusion that the rate of unprovoked seizures following Prevnar being no greater than the background rate, is more likely the higher the background rate.

However, assuming equivalence, a more meaningful comparison would be with Prevnar vaccinees from birth to age sixteen, with an unprovoked seizure rate one-third of that of infants, resulting in a more meaningful comparison of one

^{36/} Respondent points out that Dr. Kinsbourne’s observations about the Camfield data applying to all seizures, not just “unprovoked” seizures, was mistaken. The Camfield report of the overall incidence of childhood epilepsy in the first year of life is 110 per 100,000 doses. Epilepsy was defined in the report as one or more “unprovoked” seizures, a definition that excludes seizures with fever. The Camfield statistics cited are for the background rate of initial unprovoked seizures. Dr. Kinsbourne’s error in this instance does not alter the court’s conclusions.

unprovoked seizure per million children in the general population (Camfield data), with 2.3 instances of unprovoked seizures following a Prevnar vaccination (Wise/VAERS report). The resulting more than two-fold increase in the rate of unprovoked seizures in the Prevnar group undermines the foundation of the special master's reasoning on this point used to reject the opinion of Dr. Wheless, Hayley's treating epilepsy specialist. In any event, Dr. Wheless cites the Wise report among several sources that corroborate his prior independent opinion – one that predates the Wise report. Dr. Wheless' opinion does not rise or fall on the validity of the Wise report. Accordingly, even without the Wise report, under Federal Circuit precedence, Dr. Wheless' causation opinion was erroneously discredited.

Moreover, the Wise data was based on doses of Prevnar – and more than one dose is recommended in a calendar year, depending on age. The Camfield data was incidences of initial seizures per year. Fundamentally, the special master's conclusion of correlations between two dissimilar populations to detract from causation theories advanced such as to nullify their reliability, was flawed. The Federal Circuit has cautioned against reliance on statistical probabilities to defeat or counter causation. *Knudsen v. Sec'y of HHS*, 35 F.3d 543, 550 (Fed. Cir. 1994). That caution applies with even more force to statistical probabilities from non-random samples of less-than-fulsome reports used to discount a treating physician's opinion.

As discussed previously, under the third prong of *Althen*, petitioners are required to establish by preponderant evidence that the forty-four hours between Hayley's Prevnar vaccination and the start of her seizures was supported by medical literature. Petitioners submitted the PDR (Pet'rs' Ex. 19)^{37/} that in clinical trials, seizures were observed within three days of vaccination. Dr. Wise reported that symptoms began within 1 week after vaccination in 86% of cases. (Pet'rs' Ex. 21 at 2.) In the primary clinical trials, seizure onset was observed within three days. (Pet'rs' Ex. 19 at 4.) Treating pediatric neurologist Dr. Wheless testified that his causation opinion was based in part on the short time from vaccination to reaction, a nod to the appropriateness of that time frame. Dr. Byers, agreed that forty-four hours was “extremely appropriate.” (Tr. 158.) Dr. Kinsbourne testified a forty-eight hour period was not “difficult.” (Tr. 378.)

^{37/} Reference in briefing to this as a package insert is not clear.

“[T]he proximate temporal relationship prong requires preponderant proof that the onset of symptoms occurred within a time frame 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 (citing *Pafford*, 451 F.3d at 1358). *See Althen*, 418 F.3d at 1281 (equating “proximate temporal relationship” with “medically acceptable temporal relationship”). The onset of Hayley’s seizures, within two days of vaccination, was clearly within these time frames and the special master’s reliance on, and adoption of, a time frame of anaphylaxis, was erroneous.

As with the court’s findings of error in the special master’s findings concerning the time between Hayley’s vaccination and the extension of the duration of her seizures, petitioners claim the special master further erred in concluding the temporal requirements between the vaccination and onset of seizures were not met. Specifically, the special master reasoned that 44 hours was too long for “anaphylaxis” to occur. *Graves I*, 2008 WL 4763730, at *15. The special master credited respondent’s expert Dr. Kohrman’s opinion that, assuming Dr. Byers’ medical theory that Prevnar activated Hayley’s innate immune system which in turn produced the IL-1 β that caused seizures, reactions in the innate immune system, like anaphylaxis^{38/} would occur within minutes; accordingly, the gap from minutes to 44 hours in Hayley’s case was not bridged. *Id.* Dr. Kohrman initially repeated his

^{38/} Anaphylaxis. . . is an extremely rare and serious allergic reaction to any number of substances. It is an acute, severe and sudden allergic reaction against a foreign protein or antigen that enters the body. The agents of anaphylactic shock are many, including proteins, vitamins or chemicals. The shock can only occur in individuals who have had prior exposure to the particular substance that promotes the shock. The prior exposure “sensitizes” the individual to that substance. When the protein or antigen is reintroduced into the body, an aberrant attempt to eliminate the substance may result in anaphylactic shock. An individual may be exposed to a particular substance for years before manifesting signs of an anaphylactic reaction, as has been known to happen with penicillin. The shock can manifest itself in several ways, affecting the heart, respiratory system or skin. Penicillin, anesthetics, peanuts, seafoods, and stinging insects are the most common and serious sources of anaphylactic producing agents.

Mills v. United States, 764 F.2d 373, 378 (5th Cir. 1985) (citation omitted); *see also* 42 C.F.R. 100.3(b)(1).

opinion that an immunological response would present “more likely as anaphylactic shock and death” (Resp’t’s Ex. O at 3, ECF No. 108), a statement Dr. Byers characterized as “nothing short of breathtaking,” prompting Dr. Kohrman to admit that anaphylaxis “was probably the wrong word.” (Tr. 553, ECF No. 132). As a result, the special master’s discount of medical theories because of the lack of anaphylactic reaction, an argument abandoned by respondent, lacks record support. The special master’s remand decision did not, however, amend the finding in *Graves I* that cited Hayley’s lack of an anaphylactic reaction to the vaccine was a reason to discount petitioner’s causation theory.

CONCLUSION

For the reasons stated herein, the court concludes that on the record as a whole, petitioners presented sufficient evidence to meet the Vaccine Act’s preponderant standard for causation of the biological plausibility of the Prevnar vaccine triggering the onset of seizures, as well as increased duration and intractability of seizures, supported by reliable medical literature and expert testimony including that of Dr. Wheless, Hayley’s treating physician.

The record evidence established a medical theory causally connecting the Prevnar vaccination with the instigation as well as the duration and intractability of the seizures which resulted in Hayley’s death. A logical sequence of cause and effect was established that the Prevnar vaccine did cause the instigation of Hayley’s seizures and the increased duration and intractability within an appropriate time frame.

Accordingly, petitioners’ Motion for Review (ECF No. 93) is **GRANTED**. The decisions of the special master dated October 14, 2008 and September 21, 2010 are **SET ASIDE** and replaced by the court’s own findings of fact and conclusions of law. 42 U.S.C. § 300aa-12(e)(2)(B). Based upon those findings and conclusions, the court determines that entitlement has been proven, and the case is **REMANDED** for a determination by the special master of the compensation due petitioners.

It is so **ORDERED**.

s/ James F. Merow

James F. Merow
Senior Judge