

IN THE UNITED STATES COURT OF FEDERAL CLAIMS

OFFICE OF SPECIAL MASTERS

WALTER RAY GRAVES and LISA GRAVES *

as representatives of the estate of *

HAYLEY NICOLE GRAVES, deceased, *

Petitioners, *

v. *

SECRETARY OF HEALTH *

AND HUMAN SERVICES, *

Respondent. *

No. 02-1211V
Special Master Christian J. Moran

Filed: October 14, 2008

entitlement, Prevnar, seizures
without fever, death

Richard Gage, Esq., Richard Gage, P.C., Cheyenne, Wyoming, for Petitioner;
Lisa A. Watts, Esq., United States Department of Justice, Washington, D.C., for Respondent.

PUBLISHED DECISION DENYING ENTITLEMENT*

Walter Ray Graves and Lisa Graves, representatives of the estate of their daughter, Hayley, claim that Prevnar, a pneumococcal vaccine, caused Hayley’s death. The Graves seek compensation for Hayley’s death, pursuant to the National Childhood Vaccine Injury Act, 42

* Because this published decision contains a reasoned explanation for the special master's action in this case, the special master intends to post it on the United States Court of Federal Claims's website, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (Dec. 17, 2002).

All decisions of the special masters will be made available to the public unless they contain trade secrets or commercial or financial information that is privileged and confidential, or medical or similar information whose disclosure would clearly be an unwarranted invasion of privacy. When such a decision or designated substantive order is filed, a party has 14 days to identify and to move to delete such information before the document’s disclosure. If the special master, upon review, agrees that the identified material fits within the banned categories listed above, the special master shall delete such material from public access. 42 U.S.C. § 300aa–(12)(d)(4); Vaccine Rule 18(b).

U.S.C. §§ 300aa-1 et seq. (2006). A preponderance of the evidence establishes that they are not entitled to compensation.

I. Factual History

Hayley was born on November 4, 1999. Exhibit 14 (birth records). During her hospitalization shortly after birth, she was screened for certain problems. Her results were normal. The tests, however, did not screen for biotinidase. Exhibit 14 at 21.

At two months old, Hayley received a set of vaccines. She did not have an adverse reaction to them. Hayley had another set of vaccines at age four months. Exhibit 1 at 8, 21.

During her four month visit, Hayley's pediatrician, Dr. Harston, noted that she could not move her head to the left. Dr. Harston diagnosed Hayley as having torticollis and prescribed physical therapy. Exhibit 1 at 16. Torticollis is "a contracted state of the cervical muscles, producing twisting of the neck and an unnatural position of the head." Dorland's Illustrated Medical Dictionary (30th ed. 2003) at 1924.

At six months old, Hayley continued to hold her head to the left. She also received her first dose of the Prevnar vaccine. Exhibit 1 at 23.

On August 8, 2000, when Hayley was nine months old, Dr. Harston determined that her gross motor development was delayed.¹ Hayley rolled over occasionally. However, her parents informed Dr. Harston that Hayley did not crawl and she did not sit independently for long periods of time. Hayley babbled and could say a few words. Exhibit 1 at 31; see also exhibit 2 at 5

¹ When Dr. Kinsbourne and Mr. Graves testified they challenged Dr. Harston's determination that Hayley was delayed. However, resolving this dispute is not necessary.

(hospital admission records, dated August 10, 2000, describing Hayley's development). Dr. Harston referred Hayley for physical therapy. Exhibit 1 at 31.

At this same visit, Hayley received the second dose of Prevnar and the third dose of the hepatitis B vaccine. Exhibit 1 at 29, 31, 33. The hepatitis B vaccine is not a factor in this case. Tr. 73 (Dr. Kinsbourne), 287 (Dr. Wheless).

On August 10, 2000, Hayley had a left arm and leg focal seizure. During the seizure, Hayley remained alert and drank some formula from her bottle. The Graveses brought Hayley to Cook Children's Medical Center emergency room. Exhibit 2 at 1, 5.

At the emergency room, Hayley was given anti-seizure medication. A lumbar puncture indicated that her cerebrospinal fluid contained "2 white cells and no red cells, protein of 96, and glucose of 41." Exhibit 2 at 5. An electroencephalogram (EEG) showed "ongoing electrical seizure activity emanating from right central brain regions." Exhibit 2 at 15.

In the Cook County Pediatric Intensive Care Unit, Hayley was evaluated by Dr. Brian Ryals, a pediatric neurologist. An EEG continuously monitored Hayley and she received medication to control her seizures. Exhibit 2 at 14. Eventually, Hayley had tests done on her urine, blood, and cerebrospinal fluid. All tests came back negative, meaning that she did not have an infectious disease. A laboratory test also indicated that Hayley was not infected with herpes. Exhibit 2 at 3. During this time, the Graveses did not report that Hayley had a fever. Tr. 144.

Dr. Ryals noted that Hayley's family was concerned that her vaccinations may have caused her seizures. However, Dr. Ryals did not express an opinion as to whether the

vaccinations were the cause of Hayley's injuries. The Graveses wanted Hayley evaluated for epilepsy and Dr. Ryals concurred. Exhibit 2 at 3.

Consequently, on August 29, 2000, Hayley was transferred from Cook County Medical Center to Hermann Hospital. Although Hermann Hospital has an epilepsy center, Hayley was admitted to the pediatric intensive care unit. Hayley remained at Hermann Hospital until she died on September 24, 2000. Exhibit 10B at 119.

The details of her nearly one-month stay in Hermann Hospital are generally not relevant to determining whether the vaccination caused Hayley's seizures. It is sufficient to note that Hayley's doctors attempted several different therapies to stop the seizures. These efforts were not successful. Her doctors also searched for causes of the seizures. One pediatric neurologist, whose name is not legible, stated a "possible vaccine related CNS [central nervous system] syndrome may need to be considered." Exhibit 10B at 68 (entry, dated September 13, 2000). On September 14, 2000, other neurologists, whose names also are not legible, stated that Hayley had "seizures of unknown etiology" and expressed a "doubt" that "infection [was the] underlying pathology." Exhibit 10D at 327. Another pediatrician noted, two days later, that the "etiology of encephalitis remains unknown." Exhibit 10B at 75. Despite their investigations, Hayley's doctors could not identify a cause of her seizures.

While the doctors were considering different possibilities of Hayley's seizures, a doctor ordered a biotinidase test. However, the result of this test was not within the records of Hermann Hospital. See exhibit 10, passim. Because the result of this test could have shown that the vaccine was not the cause of Hayley's seizures, a particular effort was made to obtain the results.

A custodian of records for Hermann Hospital stated that the results of the biotinidase test could not be found. Exhibit 30 (affidavit, dated Aug. 23, 2007).

An autopsy was performed on Hayley on September 29, 2000. The pathologist concluded that Hayley “died as a result of hypoxic encephalopathy which reportedly occurred following a seizure which developed following a meningitis [sic] vaccine.” Exhibit 6 at 6.

Slides from Hayley’s autopsy were also examined by a neuropathologist, approximately one year later. The neuropathologist found “severe, diffuse Alzheimer type 2 astrocytes, . . . mild neuronal loss and gliosis, basal ganglia, [and] [m]ild cerebral edema.” Exhibit 7 at 2. A pediatric pathologist, Dr. Virginia Anderson, whom respondent retained during this litigation, essentially agreed with these findings. Exhibit A.

II. Procedural History

The petition and seven exhibits were filed on September 16, 2002. The Graveses periodically filed additional medical records throughout 2003.

Respondent filed its report, pursuant to Vaccine Rule 4, on December 8, 2003. In this report, respondent indicated that the Graveses were not entitled to compensation. In particular, respondent noted that the Graveses had not submitted a medical opinion from a qualified expert that the vaccine caused Hayley’s death. Resp’t Rep’t at 14. Respondent also observed that Hayley’s development before she received the August 8, 2000 vaccinations was not normal. Id. at 16. Finally, respondent presented a report from Dr. Virginia Anderson, a pediatric pathologist. Dr. Anderson believes that the vaccinations did not cause Hayley’s death. Exhibit A at 2.

Following the filing of respondent’s report, no substantive activity took place in this case for several years. During this time, the Graveses were attempting to retain an expert witness to

offer an opinion in support of their case. At least some of the delay was attributable to financial problems experienced by the Graveses.

Approximately four years later, the Graveses filed reports from two doctors, Dr. Marcel Kinsbourne, a neurologist, and Dr. Vera Byers, an immunologist. Exhibits 15 & 17. The Graveses filed supporting literature. They also filed a supplemental expert report from Dr. Kinsbourne, exhibit 29, on February 15, 2007.

After the Graveses filed their expert materials, respondent presented a report from another doctor, Dr. Michael Kohrman, a neurologist, on April 27, 2007. Exhibit C. Respondent later filed supporting articles.

Due to scheduling conflicts, a hearing was held in three sessions. The first hearing was held in Chicago, Illinois, on December 20, 2007. During this hearing, Hayley's father, Dr. Kinsbourne, and Dr. Byers testified. The second hearing was held by telephone on February 22, 2008, during which Dr. Kohrman testified. A third session was held on July 21, 2008, to obtain the testimony of Dr. Wheless. After Dr. Wheless testified, Dr. Kinsbourne, Dr. Byers, and Dr. Kohrman each testified.

After the third session of the hearing, the parties stated that they did not want to file briefs. With the filing of the transcript, the case is ready for adjudication.

III. Analysis

A. Summary Of Expert Opinions

Petitioner's expert, Dr. Kinsbourne, believes that the Prevnar vaccination caused Hayley to develop seizures. Dr. Kinsbourne opines that Prevnar can cause seizures. For this proposition, Dr. Kinsbourne relies upon the opinion of Dr. Byers and also an article by Robert P.

Wise et al., which was submitted as exhibit 21. While Dr. Kinsbourne acknowledges that Hayley's motor development was delayed, he also notes that Hayley "exhibit[ed] no abnormal neurological signs and had not had seizures" before her vaccinations. Dr. Kinsbourne also observes that "no metabolic or mitochondrial disorder" that could explain Hayley's seizures was identified. Thus, Dr. Kinsbourne concludes that "Pevnar, having been shown to be a potential cause of seizures, is most likely to have caused the onset of the epilepsy that ultimately caused Hayley's death." Exhibit 29.

As stated, a foundation for Dr. Kinsbourne's opinion is that Pevnar can cause seizures and for this postulate, Dr. Kinsbourne relies upon Dr. Byers. Dr. Byers explains that Pevnar, like other pneumococcal vaccines, produces a reaction in the immune system including a cytokine known as interleukin 1 β . Dr. Byers cites a study by Celine Dubé et al., which was filed as exhibit 23, that shows in mice, interleukin 1 β can produce seizures even without a fever. Thus, Dr. Byers concludes that Pevnar can induce seizures without fever (afebrile). Exhibit 17.

Respondent's expert, Dr. Kohrman, disagrees with both Dr. Byers and Dr. Kinsbourne. Dr. Kohrman opines that the Pevnar vaccination did not cause Hayley's seizures. Dr. Kohrman believes that the literature cited by Dr. Byers does not support her assertion that Pevnar can cause afebrile seizures. In addition, Dr. Kohrman suggests that if Pevnar were going to cause a seizure in Hayley, the adverse event would have developed following the first time Pevnar was administered to Hayley. Exhibit C at 5-6.

In regards to Dr. Kinsbourne, Dr. Kohrman asserts that Dr. Kinsbourne "does not acknowledge the multiple neurologic problems [Hayley] displayed prior to her vaccination." Exhibit C at 4. Dr. Kohrman believes that Hayley's symptoms are consistent with a disease

called multiple carboxylase deficiency, which is “the most likely etiology for Hayley’s developmental delay and seizure disorder.” Id. at 6 (capitalization changed without notation).

B. Elements of Petitioner’s Case

The Federal Circuit stated the elements a petitioner must establish to be entitled to compensation. The petitioner’s

burden is to show by preponderant evidence that the vaccination brought about [the] injury by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury.

Althen v. Sec’y of Health and Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005). Proof of medical certainty is not required; a preponderance of the evidence suffices. Bunting v. Sec’y of Health and Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991).

1. A Medical Theory Causally Connecting the Vaccination and the Injury

The Graveses fail to establish, by a preponderance of the evidence, a medical theory causally connecting the vaccination and injury. Although the Graveses have offered a theory, the theory is not reliable. Thus, they are not entitled to compensation.

a. Standards To Evaluate A Medical Theory

The theory offered by the Graveses must be reliable. Knudsen v. Sec’y of Health & Human Servs., 35 F.3d 543, 548 (Fed. Cir. 1994). To evaluate the reliability of the expert’s testimony, special masters may use the broad standards set forth in Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 589 (1993). Terran v. Sec’y of Health & Human Servs., 195 F.3d 1302, 1316 (Fed. Cir. 1999) (affirming special master’s use of Daubert in vaccine

program cases). After Terran, decisions from judges of the Court of Federal Claims have consistently cited to Daubert when reviewing decisions of special masters. E.g., De Bazan v. Sec’y of Dept. of Health & Human Servs., 70 Fed. Cl. 687, 699 n.12 (2000) (“A special master assuredly should apply the factors enumerated in Daubert in addressing the reliability of an expert witness’s testimony regarding causation.”), rev’d on other grounds, 539 F.3d 1347 (Fed. Cir. 2008); Campbell v. Sec’y of Dept. of Health & Human Servs., 69 Fed. Cl. 775, 781 (2006); Piscopo v. Sec’y of Health & Human Servs., 66 Fed. Cl. 49, 54 (2005).

Daubert lists several non-exhaustive factors that may be considered in assessing the reliability of the expert’s opinion. Kumho Tire Co., Ltd. v. Carmichael, 526 U.S. 137, 149 (1999). The factors include whether the expert’s opinion is well accepted in the relevant community. Daubert, 509 U.S. at 594; see also McDowell v. Brown, 392 F.3d 1283, 1299 (11th Cir. 2004) (affirming district court’s exclusion of expert whose theory lacked “testing, peer review, a potential error rate, and general acceptance.”); Sullivan v. United States Dep’t of Navy, 365 F.3d 827, 834 (9th Cir. 2004) (reversing exclusion of expert whose theory was generally accepted).

A closely related factor is how peer-reviewed articles have evaluated a theory. This point may also be considered in weighing the value of a medical opinion. Id.; see also Merck & Co., Inc. v. Teva Pharmaceuticals USA, Inc., 395 F.3d 1364, 1374 (Fed. Cir. 2005); Libas v. United States, 193 F.3d 1361, 1366-67 (Fed. Cir. 1999); Knight v. Kirby Inland Marine Inc., 482 F.3d 347, 354 (5th Cir. 2007) (stating a lack of textual support may “go to the weight, not the admissibility” of the expert’s testimony); Waleryszak v. Sec’y of Health & Human Servs., 45 Fed. Cl. 573, 578-79 (1999), appeal dismissed, 250 F.3d 753 (Fed. Cir. 2000). Petitioners are not

required to produce articles to establish the reliability of their expert's opinions. Althen, 418 F.3d at 1279.

b. Medical Theory Offered by the Graveses

The two neurologists retained by the Graveses believe that Plevnar 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 Plevnar in the Physicians' Desk Reference (PDR). These articles, however, do not show that Plevnar causes seizures in the absence of fever.

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

(1) Dr. Kinsbourne and Dr. Wheless

Dr. Kinsbourne was trained as a neurologist. Exhibit 16 (curriculum vitae of Dr. Kinsbourne). But, Dr. Kinsbourne rarely sees patients as a neurologist. Instead, Dr. Kinsbourne works as a professor of psychology. Tr. 30. He has testified in many, many cases in the Vaccine Program on behalf of petitioners. Simon v. Sec'y of Health & Human Servs., No. 05-941V, 2008 WL 623833 (Fed. Cl. Spec. Mstr. Feb. 21, 2008).

Like Dr. Kinsbourne, Dr. Wheless was trained in neurology. But, their professional careers are different. Dr. Wheless continues to practice neurology and is an expert in epilepsy, who is frequently invited to speak at conferences around the world. Exhibit 44 (curriculum vitae); tr. 269-70. Dr. Kohrman, respondent's expert, recognizes Dr. Wheless's excellent reputation in this field. Tr. 242.

In his role as a practicing neurologist, Dr. Wheless treated Hayley while she was hospitalized at Hermann Hospital until she died. Tr. 271. Because Dr. Wheless treated her, his

opinions must be considered as part of the record as a whole. Capizzano v. Sec’y of Health & Human Servs., 440 F.3d 1317, 1326 (Fed. Cir. 2006).

Whether Dr. Wheless believed, while he was treating Hayley, that the Prevnar vaccine caused her seizures is not clear. During the time that Dr. Wheless treated Hayley, he did not express an opinion that the Prevnar vaccine caused her epilepsy. Tr. 285. This omission is telling because Dr. Wheless was aware that Hayley was vaccinated only two days before she had her first seizure. Exhibit 3 at 3 (report dated August 29, 2000, stating “etiology [is] uncertain”); see also exhibit 10B at 68 (progress note saying “possible vaccine related [central nervous system] syndrome.”) However, Dr. Wheless testified that while he was treating Hayley, he suspected that the Prevnar vaccine was the cause of her seizures. Tr. 272, 285, 299.

Years after Hayley’s unfortunate death, the Graveses contacted Dr. Wheless and asked whether Dr. Wheless could provide an expert opinion. Tr. 288. Dr. Wheless agreed to do so and is being compensated for the time he spent on his opinion. Tr. 300. In these circumstances, Dr. Wheless’s opinion stands on the same ground as any other expert retained by a party in litigation.¹

Dr. Wheless and Dr. Kinsbourne rely on the same materials for their opinion that Prevnar can cause seizures without a fever. They primarily rely upon an article by Wise. Additionally, Dr. Kinsbourne cites to the entry for Prevnar in the PDR. For the reasons explained below, these two articles do not show that Prevnar causes seizures without a fever.

¹ 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. Kohnman, who hold opposite opinions, also appeared honest and sincere.

(a) Wise Article

The primary support for Dr. Kinsbourne's opinion that Prevnar can cause seizures without a fever is the Wise article. Exhibit 15 at 3; see also tr. 39 (Dr. Kinsbourne's testimony discussing Wise article). It also supports Dr. Wheless's testimony. Exhibit 43 at 2; see also tr. 273, 288-90, 293-94 (Dr. Wheless's testimony).

Because the Wise article is a primary support for opinions from Dr. Kinsbourne and Dr. Wheless, it is discussed in some detail. This level of analysis is appropriate because "[a]n expert opinion is no better than the soundness of the reasons supporting it." Perreira v. Sec'y of Health & Human Servs., 33 F.3d 1375, 1377 n.6 (Fed. Cir. 1994). An examination of the article indicates that it does not stand for the proposition that petitioners' experts have assigned to it.

The Wise article "summarizes data from the Vaccine Adverse Event Reporting System (VAERS) in the first 2 years after [Prevnar] licensure." Exhibit 21 (Robert P. Wise et al., Postlicensure Safety Surveillance for 7-Valent Pneumococcal Conjugate Vaccine, 292 J. Amer. Med. Ass'n 1702 (2004)) at 1. The source of the raw information by itself leads to some questions about any conclusion. Information extracted from the VAERS database may not be reliable because information entered into the VAERS database may not be accurate. Thus, the United States Court of Federal Claims "uniformly has upheld the . . . concerns about the reliability of VAERS data." Analla v. Sec'y of Health & Human Servs., 70 Fed. Cl. 552, 558 (2006) (citing cases). The authors, themselves, recognize the limited value of information from the VAERS database. They state that "Reported events may be a small fraction of all that occur and they frequently defy facile assessment of whether vaccinations played a causal role. Nevertheless, the potential to detect important clues from patterns among collected reports

warrants careful surveillance.” Exhibit 21 at 2. Dr. Wheless also realizes that the Wise article is not based upon “ideal” data, the VAERS reports. Tr. 312-13.

In the Wise study, the researchers attempted to analyze whether people were reporting adverse events associated with Prevnar. In approximately three-fourths of all cases in which people reported some adverse event following the Prevnar vaccine, the person received at least one other vaccine. Exhibit 21 at 2. This confluence lessens confidence in drawing conclusions solely about Prevnar because the other vaccine could have caused the adverse event associated with Prevnar. (The presence of a possible alternative cause (the other vaccine) is known as a “confounding factor.” Tr. 85-87, 383 (Dr. Kinsbourne’s testimony).)

The researchers performed a more detailed study of 98 cases in which seizures were reported after Prevnar. Exhibit 21 at 2. Of these 98 cases, 79 patients reported having a previous history of having seizures or having a fever at the time of seizure. This group of 79 patients can be eliminated because fevers and past history of seizures are associated with seizures. Id. at 7. The remaining 19 people had neither a fever nor a prior history of seizures. Exhibit 21 at 5. This group of 19 individuals is comparable to Hayley. See tr. 138 (Dr. Byers’s testimony indicating that Hayley is not like people who had a seizure with a fever).

The incidence of 19 seizures following Prevnar is not by itself a meaningful number because a denominator must be supplied. Cf. GHS Health Maintenance Org., Inc. v. United States, 536 F.3d 1293, 1302 (Fed. Cir. 2008). After some computations, the rate of reported seizures turns out to be 2.6 seizures per million doses of Prevnar. Tr. 234-35; see also tr. 257-58 (explaining that another assumption would change the incident rate to approximately two seizures per ten million doses of Prevnar). Approximately two seizures per million doses is very

close to the overall expected rate of seizures during the first year of life in general. Tr. 183-87, relying on Exhibit N (Peter R. Camfield and Carol S. Camfield, Pediatric Epilepsy: An Overview in Pediatric Neurology, Principles and Practice (Kenneth E. Swaiman and Stephen Ashwal, ed., 3d Ed.)). Thus, an analysis of the numbers from the Wise article does not indicate that Prevnar caused any seizures.

The authors of the Wise study do not draw the conclusion that Prevnar caused seizures without a fever. In Dr. Kinsbourne's words, the authors "don't purport that this is causal proof." Tr. 67; accord tr. 244 (testimony of Dr. Kohrman). Dr. Wheless recognizes that the Wise study is not an epidemiological study that establishes causation. Tr. 289-90.

Despite these limitations, Dr. Wheless maintains that Wise study "not only raises a concern, but when that concern fits with kind of an understanding of how vaccines work and immunologic targets that are based in the nervous system, it [the Wise study] helps put that puzzle together as far as saying this is possible to occur as a causation mechanism." Tr. 313. Similarly, Dr. Kinsbourne believes that the Wise study contains meaningful data. Tr. 69, 72. In rebuttal, Dr. Kinsbourne asserted that Dr. Kohrman erred when comparing, on one hand, the number of seizures after Prevnar as reported by Wise, and, on the other hand, the number of seizures that occur in the first year of life. Tr. 372-74. Dr. Kinsbourne criticizes Dr. Kohrman's use of the chapter by Camfield and Camfield because, according to Dr. Kinsbourne, "the Camfield figures are not limited to seizures without fever. . . . So what [Dr. Kohrman is] comparing is the incidence of afebrile seizures after Prevnar with the incidence of any kind of seizure normatively." Tr. 373-74.

However, Dr. Kinsbourne misinterprets the Camfield data. The chapter is about pediatric epilepsy, which means that a “child has had two or more unprovoked seizures. . . . Unprovoked implies that there has been no concurrent illness Thus recurrent seizures . . . associated . . . with fever do not qualify for the diagnosis of epilepsy.” Exhibit N at 629. The Camfields provide an incidence of epilepsy. Id. Given their definition of epilepsy, the incident rate necessarily excludes seizures with fever. Tr. 404-05. Consequently, Dr. Kohnman’s use of the statistics from Camfield is valid. His opinion – that the Wise article does not show a higher rate of seizures without fever after Prevnar – is persuasive.

In contrast, the conclusion drawn by Dr. Kinsbourne and Dr. Wheless – that the Wise article shows that Prevnar causes seizures in the absence of fever – is not supported. Although petitioners in the Vaccine Program may rely upon circumstantial evidence, Althen, 418 F.3d at 1280; the evidence being considered must be capable of being interpreted in a way offered by the petitioners. See United States v. Patel, 370 F.3d 108, 113 (1st Cir. 2004) (defining “circumstantial evidence”); Fedorczyk v. Caribbean Cruises Lines, Ltd., 82 F.3d 69, 74 (3rd Cir. 1996) (same).

The Wise article does not serve as a reliable basis for finding that Prevnar causes seizures without a fever. Therefore, the other literature supplied by Dr. Kinsbourne will be considered.

(b) PDR Entry for Prevnar

Besides the Wise article, Dr. Kinsbourne cites to the PDR entry for Prevnar. Exhibit 15 at 3; see also tr. 36 (Dr. Kinsbourne’s testimony discussing PDR). The Graveses filed the entry for Prevnar from the PDR as exhibit 19.

The PDR does not provide any useful information about whether Prevnar can cause seizures without fever. This is primarily due to a confounding factor – the children in a trial who experienced a seizure also received either the DTaP vaccine or the DTP vaccine. Exhibit 19 at 4. Dr. Kinsbourne agrees that the study reported in the PDR is “quite inconclusive.” Tr. 38; accord tr. 85.

For the reasons discussed above, the Wise study does not constitute a basis for a persuasive expert opinion. Both Dr. Kinsbourne and Dr. Wheless draw a conclusion from the Wise article, that Prevnar can cause seizures in the absence of fever. However, the authors of the study did not make this conclusion and the data does not support it. Likewise, the PDR entry does not provide meaningful information about whether Prevnar can cause seizures without a fever. Consequently, the Graveses have not established, by a preponderance of the evidence, that the theory offered by Dr. Kinsbourne and Dr. Wheless is reliable. Thus, the next step is to determine whether Dr. Byers’s opinion satisfies the Graveses’ burden.

(2) Dr. Byers’s Opinion

(a) Overview and Background

Dr. Byers believes that Prevnar can cause seizures without a fever. Exhibit 17 (report of Dr. Byers) at 6; tr. 99, 139. Thus, her opinion underlies Dr. Kinsbourne’s opinion. Exhibit 15 (report of Dr. Kinsbourne) at 3; tr. 73.

Dr. Byers concludes that Prevnar can cause seizures without a fever by looking at several different articles, which are discussed below. The general problem with Dr. Byers’s analysis is that it isolates some portion of the articles without placing them in the context of this case. Thus, Dr. Byers’s opinion is not reliable.

Before analyzing the articles on which Dr. Byers's opinion is based, some context for her opinion must be provided. 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).

Against this backdrop, Dr. Byers offers her opinion that Prevnar can cause seizures without a fever. The more detailed explanation for the steps underlying Dr. Byers's theory that

Pevnar caused Hayley's seizures even though Hayley did not have a fever are as follows. The Pevnar vaccine stimulated Hayley's innate immune system to produce a response. Tr. 100. One response to Pevnar is to produce various cytokines. Cytokines are cells that deliver messages to other parts of the immune system. Tr. 189 (Dr. Kohrman); Dorland's Illustrated Medical Dictionary (30th Ed. 2002) at 469. The specific cytokine identified by Dr. Byers as playing an important role is one known as interleukin 1 β (commonly abbreviated as IL-1 β). Tr. 120. This description is not disputed by respondent or respondent's expert, Dr. Kohrman. Tr. 189-91, 392.

The next step, however, is more contentious. Dr. Byers believes that the IL-1 β , which Hayley produced, accumulated in Hayley's brain. When a sufficient amount of IL-1 β accumulated in Hayley's brain, the IL-1 β caused Hayley to have a seizure. Dr. Byers cited to various articles about this point — whether IL-1 β can cause seizures.

Although the Graveses were not required to use medical literature as objective confirmation of the reliability of Dr. Byers's theory, Althen, 418 F.3d at 1279; peer-reviewed medical articles are one permitted way to determine the reliability and persuasiveness of an expert's opinion. Thus, because the Graveses have opted to support Dr. Byers's theory with medical articles, these articles are analyzed in the next section. See 42 U.S.C. § 300 aa-13(a)(1) (requiring a decision "on the record as a whole.").

(b) Specific Articles

Dr. Byers primarily relied upon five articles. As explained below, the articles do not support the use given to them by Dr. Byers.

i) **Haverman Exhibit 40**

Dr. Byers cites to an article by Haverman to establish a preliminary point. According to Dr. Byers, Haverman shows that either the induction of hyperthermia or the stimulation of toll-like receptors (part of the immune system) can cause the production of IL-1 β . Tr. 107-09.² The article is actually more restricted than Dr. Byers's interpretation of it.

Haverman compared the results of heating an entire rat with the results of heating the right hind leg of other rats. Haverman was looking to see whether the difference in the extent of heating caused the rats to produce a different amount of cytokines. The results showed that rats who were treated by whole body hyperthermia produced more interleukin 1 than rats who were not so heated. Exhibit 40 (J. Haverman, A.G. Geerdink and H.M. Rodermond, Cytokine Production after Whole Body and Localized Hyperthermia, 12 (No. 6) Int. J. Hyperthermia 791 (1996) at 794, figure 1). The results also showed that rats that were heated only in their right hind leg did not produce a significant amount of interleukin 1. Id. at 795, figure 2; see also tr. 246.

The difference in these two experiments undermines Dr. Byers's opinion. The first experiment shows that heating (which can be analogous to fever) prompts the production of interleukin 1 when the heating occurs over the rats' "whole body." The second experiment shows that when the heating is localized to only one part of the rat, interleukin 1 is not increased. See tr. 191-94.

² Although the transcript sometimes uses the word "hypothermia," the correct word is "hyperthermia," meaning heating.

Dr. Byers attempts to use this paper to establish what prompts the production of interleukin 1. Tr. 107-09. (Although Dr. Byers mentions that lipopolysaccharides can stimulate toll-like receptors to produce interleukin 1, the article focuses on hyperthermia.) Dr. Byers opines that hyperthermia can lead to the production of interleukin 1. The article does support this proposition, but only when the hyperthermia affects the rats' entire body. Dr. Byers did not explain why a reaction based on the organism's entire body is comparable to a situation in which the person's entire body is not affected. For Hayley, the vaccination did not produce a systemic response, which could be compared to the whole body heating in Haverman's first experiment. Consequently, the Haverman article does not establish the reliability of Dr. Byers's opinion.

ii) Vezzani, Exhibit 28 and Exhibit 48

Dr. Byers also cited to two papers by Annamaria Vezzani. The first paper was filed as exhibit 28. Exhibit 28 (Annamaria Vezzani, Interleukin-1 β Immunoreactivity and Microglia Are Enhanced in the Rat Hippocampus by Focal Kainate Application: Functional Evidence for Enhancement of Electrographic Seizures, 19(12) J. of Neuroscience 5054 (1999)). The second paper was filed as exhibit 48. Exhibit 48 (Annamaria Vezzani et al., Functional Role of Inflammatory Cytokines and Antiinflammatory Molecules in Seizures and Epileptogenesis, 43 (Supp. 5) Epilepsia 30 (2002)).

In the experiment reported in exhibit 28, the researchers examined the amount of IL-1 β a rat produced after rats were injected with kainic acid. Exhibit 28 at 5055. Kainic acid is known to induce seizures without producing a fever. Tr. 114, 117 (Dr. Byers)³, 135-36, 197; see also

³ Although the term "tannic" sometimes appears in the transcript, the correct word is "kainic."

exhibit 28 at 5056. Researchers gave some rats IL-1Ra, which blocks IL-1 β . Tr. 116 (Dr. Byers); see also exhibit 28 at 5060-62. The researchers concluded that “focal intra-hippocampal application of kainic acid in rats inducing EEG seizures . . . is associated with a rapid increase in the levels of IL-1 β in the hippocampus presumably in the activated microglia cells.” Exhibit 28 at 5062.

The results from this experiment are presented in Table 1. Table 1 shows that rats that received IL-1Ra (meaning that their ability to process IL-1 β was blocked) experienced the same number of seizures as rats that received IL-1 β but not IL-1Ra. Id. at 5062 (Table 1). This similarity indicates that IL-1 β did not cause seizures. Tr. 196 (Dr. Kohrman). However, the seizures in rats with the IL-1 β lasted for a longer amount of time. Exhibit 28 at 5062 (Table 1).

In exhibit 48, the researchers induced seizures in rats using kainic acid or electroshock. Exhibit 48 at 31; tr. 202. Again, kainic acid is known to induce seizures. Tr. 135-36, 201. The researchers concluded that “seizures in rodents rapidly and reversibly induce inflammatory cytokines in glia in the hippocampus.” Exhibit 48 at 34.

Dr. Byers maintains that the two Vezzani papers show that kainic acid produces IL-1 β , and IL-1 β induces seizures. Tr. 115. But, this opinion is not persuasive.

The more persuasive opinion is that IL-1 β does not cause seizures. The cause of the seizures is the kainic acid (or the electroshock). The seizures prompt the body to produce IL-1 β as a way to recover from the seizures. Tr. 195-202.

Dr. Kohrman’s interpretation of the reports is more in line with what Vezzani et al. reported. The first article states “application of kainic acid in rats inducing EEG seizures . . . is associated with a rapid increase in the levels of IL-1 β .” Exhibit 28 at 5062. Similarly, the

second article states “seizures in rodents rapidly and reversibly induce inflammatory cytokines.” Exhibit 48 at 34 (emphasis added). These statements imply, if not actually directly indicate, that the sequence is an injection of kainic acid, then the production of seizures, then an increase in IL-1 β . The sequence proposed by Dr. Byers (an injection of kainic acid, then an increase in IL-1 β , then the onset of seizures) is not well-supported. Tr. 342-43.

Because Dr. Byers’s opinion that the Vezzani papers show IL-1 β causes seizures is not supported by an examination of the papers themselves, addressing a subsidiary point is not necessary. On rebuttal, Dr. Byers disagreed with testimony from Dr. Kohrman earlier in the hearing about where the IL-1 β is produced. Dr. Kohrman’s opinion was that IL-1 β is produced locally (meaning at the site of the vaccination) and then travels to the brain. However, Dr. Byers clarified that a vaccination can stimulate macrophages to produce IL-1 β and that these macrophages travel through the blood system to the brain where they produce IL-1 β . Tr. 327, 338. It is not entirely clear whether Dr. Kohrman agrees with this point. However, whether the body produces IL-1 β locally or in the brain is not relevant because the IL-1 β is not the cause of seizures.

iii) Dubé, Exhibit 23

The next significant article was written by Celine Dubé (and Annamaria Vezzani, among others). Like the other two articles by Ms. Vezzani, this article explores the role of interleukin-1 β . Exhibit 23 (Celine Dubé et al., Interleukin-1 β Contributes to the Generation of Experimental Febrile Seizures, 47 Ann Neurol 152 (2005)). Dr. Byers, again, cites this article as support for her opinion that IL-1 β is the “direct cause” of a seizure. Tr. 118.

The relevance of the Dubé article is not readily apparent. The title alone indicates that the research concerned “febrile seizures.” The authors’ description of their own work confirms this focus: “we tested the hypothesis that endogenous IL-1 β contributes to the mechanisms of fever-induced seizures, and that these IL-1 β actions are independent of genetic background.” Exhibit 23 at 152. As discussed, it is well established that fevers can cause seizures. The research by Dubé explores how (the mechanism) this happens. However, Hayley Graves did not have a fever. Thus, this article on first review seems not to provide any information about whether IL-1 β causes seizures in the absence of fever.

A more detailed examination of the Dubé article reveals the following. The researchers used a group of mice that lacked the receptor to process IL-1 β and a group of wild-type mice. Exhibit 23 at 152; tr. 118, 136. Dr. Byers referred to the group that lacked the ability to process IL-1 β as “knock out mice,” because the pertinent gene had been knocked out of them. Tr. 118. The researchers heated the mice to “41°C (as during high fever).” The researchers then observed how the mice responded. Exhibit 23 at 152. The researchers believed that if IL-1 β contributed to the production of seizures with fevers, then the knock-out mice would have a different response. This belief was confirmed because the knock out mice experienced seizures at higher temperatures than the other mice. Id. at 153.

The researchers then conducted a second experiment, one that possibly has more significance to Hayley’s case. The researchers gave IL-1 β to knock out mice and wild-type mice. “[I]nfusion of high dose (116 ng) of IL-1 β to normothermic mice resulted in prolonged limbic seizures in wild-type [] mice, whereas the [knock out] mice were resistant.” The researchers concluded that “high doses (~ 100ng) of this cytokine are sufficient to generate seizures even

without increased brain temperatures.” Id. at 154; accord tr. 203-04 (Dr. Kohrman), 368-69 (Dr. Byers).

Consequently, the Dubé article does support the theory that IL-1 β can cause seizures in mice. Tr. 369-70 (Dr. Byers). However, there are problems with extending this article to Hayley’s situation. First, extrapolating from the experiments with mice to human beings is not always appropriate. See Allison v. McGhan Medical Corp., 184 F.3d 1300, 1314 (11th Cir. 1999) (stating “Daubert decisions in other courts warn against leaping from an accepted scientific premise to an unsupported one” and citing cases); In re Paoli R.R. Yard PCB Litigation, 35 F.3d 717, 779-81 (3d Cir. 1994) (discussing cases). Special Masters have recognized the limited value of animal studies. Andreu ex rel. Andreu v. Sec’y of Health & Human Servs., No. 98-817V, 2008 WL 2517179 *6 (Fed. Cl. Spec. Mstr. May 29, 2008), sustained, 2008 WL 3842915 (Fed. Cl. Jul 23, 2008); Lunn v. Sec’y of Health & Human Servs., No. 97-436V, 2000 WL 246237 *4 (Fed. Cl. Spec. Mstr. Feb. 16, 2000). Dr. Byers agrees that extrapolating from mice to humans is not always easy. Tr. 426.

Second, even if an analogy from mice to human were possible, Hayley Graves after vaccination is not comparable to the mice in the Dubé study. The mice in the Dubé study received what the authors described as a “high dose” of IL-1 β . Exhibit 23 at 154. According to Dr. Kohrman, the amount of IL-1 β used (116 nanograms), which was injected directly into the hippocampus of the mice, exceeds by many factors the amount of IL-1 β that Hayley could have produced in response to a vaccination. Tr. 204, 250-52, 395, 417. Dr. Byers agrees that IL-1 β causes a seizure only at a certain dose. Tr. 340. This difference makes the extrapolation unreliable. Henley v. Food and Drug Admin., 77 F.3d 616, 621 (2d Cir. 1996) (stating “The

pertinent animal studies in this case-showing a connection between estrogen and cancer-are not necessarily applicable to humans, particularly where the animal studies used relatively higher dosages than would normally be ingested by humans.”); Lunn, 2000 WL 246237 *4 (stating “this evidence, that extremely high body temperatures can cause hearing loss in rats, hardly constitutes significant evidence for the proposition that a temperature of 104°-105° Fahrenheit can cause human hearing loss”) (emphasis in original).

Dr. Byers has no persuasive rebuttal to Dr. Kohrman’s assertion that the amount of IL-1 β in Dubé is not comparable to what Hayley experienced. Dr. Kohrman made this point when he testified on February 22, 2008. Tr. 204, 250-52. Dr. Byers reviewed his testimony in preparation for her testimony on July 21, 2008. Tr. 320. Dr. Byers responded by stating that the concentration of IL-1 β is physiologically attainable. Tr. 328, 368-69.

However, Dr. Byers was not as persuasive as Dr. Kohrman. Special Masters are entitled to deference in their evaluations of the persuasiveness of experts. Pafford v. Sec’y of Health & Human Servs., 451 F.3d 1352, 1359 (Fed. Cir. 2006); Energy Capital Corp. v. United States, 302 F.3d 1314, 1329 (Fed. Cir. 2002) (“As for the relative weight given to the testimony of both sides’ expert witnesses, we accord the trial court broad discretion in determining credibility because the court saw the witnesses and heard their testimony.”)

Dr. Byers’s rebuttal amounts to a statement that it is possible that Hayley produced a high concentration of IL-1 β . Dr. Byers did not use the word “possible.” Rather, she said “I would disagree that the concentration of IL-1 beta is not physically attainable.” Tr. 328. However, Dr. Byers points to no evidence that would support a finding that Hayley was producing more and more IL-1 β before she had her seizure. If Hayley were producing high amounts of IL-1 β over the

course of approximately 40 hours, then there should have been some manifestation of a problem before the first seizure happened. Tr. 357 (Dr. Byers), 226, 242, 251, 254, 403-04 (Dr. Kohrman). However, she did not. Tr. 144 (Dr. Byers).

For these reasons, the Dubé article is not helpful in establishing the reliability of Dr. Beyers's opinion.

iv) Mazarati, Exhibit 42

The final article that received significant attention during the hearing is a commentary written by Andrey M. Mazarati. Exhibit 42 (Andrey M. Mazarati, Cytokines: A Link Between Fever and Seizures, 5(No. 5) Epilepsy Currents 169-170 (2005)). It is a commentary on the article by Dubé. Id.; see also tr. 205, 329.

Dr. Byers cited to the Mazarati paper to show that “[t]here is a growing realization in the neuroimmunologic community that in fact IL-1 beta has a central role in these febrile seizures as well as other kinds of seizures.” Tr. 329-30. A primary support is the diagram showing, according to Dr. Byers, that “IL-1 beta can produce fever, it can produce seizures, or it can produce both.” Tr. 330, referencing exhibit 42, figure 1; accord tr. 365.

It is not clear whether Dr. Mazarati was intending to comment upon a possible causal relationship between IL-1 β and seizures in the absence of fever. The title of the commentary is “Cytokines: A Link Between Fever and Seizures.” The commentary, which is only two pages in length, discusses afebrile seizures only in passing. In addition, Dr. Mazarati appears not to have considered whether IL-1 β produces seizures in the absence of fever only if the IL-1 β is given in a large dose. Therefore, this commentary is not persuasive evidence that the neuroimmunologic community agrees that IL-1 β can produce seizures in humans in the absence of fever.

(3) Evaluation of Petitioners' Medical Theories

The essence of the Graveses' cause of action is that Prevnar can cause seizures in the absence of fever. The evidence submitted to establish the reliability of their expert's opinions does not, in fact, establish, by a preponderance of the evidence, that the theories are reliable. Therefore, the Graveses have not met their burden of proof.

2. A Showing of a Proximate Temporal Relationship Between Vaccination and Injury

Althen also requires that petitioners establish, by a preponderance of the evidence, that there is a proximate temporal relationship between vaccination and injury. Bazan v. Sec'y of Health & Human Servs., 539 F.3d 1347, 1352 (Fed. Cir. 2008). In this case, the Graveses have not met their burden. This failure to establish the temporal relationship means that they are not entitled to compensation. Pafford, 451 F.3d at 1358-59.

To establish the appropriate temporal relationship, the Graveses rely upon the opinion of Dr. Byers. Tr. 12 (opening statement). Dr. Byers believes that the Prevnar stimulated Hayley's innate immune system.⁴ The innate immune system, principally a type of cell called a macrophage, produced so much IL-1 β that, eventually, the accumulation of IL-1 β caused Hayley's seizures. Tr. 100-01. Dr. Byers opines that 44-48 hours between vaccination and the onset of the seizures is an appropriate amount of time. Tr. 158-59.

⁴ Dr. Byers explained that her theory does not involve the adaptive immune system. Tr. 100. The adaptive immune system is involved in cases in which petitioners claim that a vaccine caused them to develop an auto-immune disorder. Tr. 335.

Dr. Byers also stated that the anamnestic response is not a factor. Tr. 358; see also tr. 209 (testimony of Dr. Kohrman describing Dr. Byers's theory).

Even setting aside the proposition that IL-1 β caused seizures without a fever, Dr. Byers's opinion about timing is not persuasive. Reactions in the innate immune system, such as anaphylaxis, occur within minutes. Tr. 241. Dr. Byers agrees with this estimate. Tr. 352.

Dr. Byers, however, believes that for Hayley, the production of IL-1 β started within minutes or hours and then continued to accumulate. This accumulation of IL-1 β necessarily took place over several hours (almost two days) before the IL-1 β triggered a seizure. Tr. 338, 352. (Dr. Kinsbourne endorses this theory, too. Tr. 378.) Of course, Dr. Byers must posit that the amount of IL-1 β increased within Hayley because the literature, especially the Dubé article discussed above, indicates that a small amount of IL-1 β does not trigger seizures.

The problem is that Dr. Byers provides no basis for thinking that IL-1 β accumulates for about two days. In the following passage, Dr. Byers admits the lack of a basis:

Q Well, if I'm to understand your theory that when Hayley got the Prevnar vaccine on August 8, 2000, that there's this cytokine response in the brain, why did it take two full days to get there?

A I think there is not any literature that I can cite to tell you this, but I can say that the animal literature indicates that IL-1 beta can act immediately or it can prolong the seizures, and I would say that that's probably what's happening.

Tr. 335; accord tr. 339. Dr. Byers's answer is telling in that she says "there is not any literature." Although Althen holds that petitioners are not required to introduce literature to support opinions offered by their experts, Althen, 418 F.3d at 1279; the opinions must be shown to be reliable in some respect.

Here, Dr. Byers's opinion about timing rests more upon conjecture than reliable scientific basis. The basic chronology of Hayley's case is that Hayley received Prevnar, did not display any

signs of an adverse reaction such as extreme fussiness, crying or a fever, and approximately 44 hours after the vaccination had her first seizure. The 44 hours of seemingly normal behavior between vaccination and onset is a gap that Dr. Byers must address. Her explanation is that the IL-1 β was accumulating. However, this explanation appears to be more a product of needing to fill a gap, than based upon any medical basis.

At best, Dr. Byers cites to a Vezzani article that shows that the production of IL-1 β starts approximately three hours after an insult (in Vezzani, the injection of kainic acid into the hippocampus). Tr. 336-42, citing exhibit 28 at 5059. Because Vezzani studied rats, this work may or may not provide meaningful information about humans, such as Hayley. Dr. Byers recognizes that the timing would need to be adjusted, tr. 338; but does not provide any basis for any adjustment. See tr. 400 (testimony of Dr. Kohrman, stating that no data “support[s] a timeframe for a seizure in Hayley’s case”).

Consequently, the Graveses have not established, by a preponderance of the evidence, that Hayley’s seizure occurred within a medically appropriate time after the Prevnar vaccination.

3. A Logical Sequence of Cause and Effect Showing That the Vaccination Was the Reason for the Injury

The remaining element from Althen is “a logical sequence of cause and effect showing that the vaccination was the reason for the injury.” Althen, 418 F.3d at 1278. The Graveses do not meet their burden on this point as well.

Section 1 and 2, above, explain why the Graveses have not met their burden of establishing, by a preponderance of the evidence, the first and third prongs listed in Althen.

Many of the reasons for finding that they have not met their burden on these prongs overlap with the deficiencies on this prong.

The primary flaw in the Graveses' proposed proof regarding the "logical sequence" is that 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.

C. Alternative Cause

Through Dr. Kohrman, respondent suggests that "the most likely etiology" for Hayley's seizures may have been a genetic deficiency in that Hayley may have lacked the ability to process biotinidase. Exhibit C at 6. A considerable amount of evidence was introduced on this topic.

Determining whether Hayley suffered from a biotinidase deficiency is not necessary because the Graveses have not otherwise established that they are entitled to compensation by meeting, by a preponderance of the evidence, the three factors in Althen. See Bazan, 539 F.3d at 1353-54.

IV. Conclusion

Hayley's death was tragic. I extend my sympathy to the Graveses for their loss.

Nevertheless, the Graveses have not established that the Prevnar vaccine caused the seizures that led to Hayley's death. Thus, they are not entitled to compensation. If a motion for review is not filed, the Clerk's Office is ordered to enter judgment in favor of respondent.

IT IS SO ORDERED.

Christian J. Moran
Special Master