In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 15-1526V

Filed: March 7, 2024

ABIGAIL SIMS *and* DANIEL SIMS, *on behalf of their deceased daughter*, A.E.S.,	*
Petitioners,	*
v.	*
SECRETARY OF HEALTH AND HUMAN SERVICES,	*
Respondent.	*

Michael G. McLaren, Esq., Black McLaren, et al., PC, Memphis, TN, for petitioners.
Voris E. Johnson, Esq., U.S. Department of Justice, Washington, DC, for respondent.

RULING ON ENTITLEMENT[1]

Roth, Special Master:

On December 15, 2015, Abigail and Daniel Sims ("petitioners") filed a petition on behalf of their minor daughter, A.E.S., for compensation under the National Vaccine Injury Compensation Program.[2] Petitioners allege that A.E.S. died on December 16, 2013, as a result of the Pediarix (DTaP/IPV/HepB), Hib, PCV13, and RotaTeq vaccinations she received that day. Petition, ECF No. 1.

After reviewing all the evidence filed herein, I find that the vaccines A.E.S. received on December 16, 2013 contributed to her death.

[1] Because this Ruling contains a reasoned explanation for the action taken in this case, it must be made publicly accessible and will be posted on the United States Court of Federal Claims' website, and/or at https://www.govinfo.gov/app/collection/uscourts/national/cofc, in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2018) (Federal Management and Promotion of Electronic Government Services). **This means the Ruling will be available to anyone with access to the internet.** In accordance with Vaccine Rule 18(b), Petitioners has 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, the undersigned finds that the identified material fits within this definition, such material will be redacted from public access.

[2] National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755. Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2012).

I. Procedural History

Petitioners filed their petition on December 15, 2015. ECF No. 1. Petitioners filed supporting medical records and affidavits over the months that followed. ECF Nos. 9, 12.

Respondent filed his Rule 4(c) Report on May 12, 2016, recommending against compensation. ECF No. 14.

Thereafter, petitioners filed additional medical records and an expert report and medical literature from Dr. Robert Shuman.[3] ECF Nos. 23, 26.

Respondent filed expert reports from Dr. Christine McCusker and Dr. Brent Harris, as well as supporting medical literature.[4] ECF Nos. 35-38. A status conference was held on October 11, 2017, during which the parties were encouraged to discuss settlement. ECF No. 39. In a status report filed on November 20, 2017, respondent advised that he intended to defend the case. ECF No. 40.

On June 15, 2018, petitioners filed an expert report and supporting medical literature from Dr. Eric Gershwin. ECF Nos. 43-46. Respondent filed a responsive expert report and literature from Dr. McCusker on September 24, 2018, and petitioners filed a supplemental report from Dr. Gershwin on December 7, 2018. ECF Nos. 50-51. On January 29, 2019, respondent filed a status report indicating that no further expert reports would be filed. ECF No. 53.

An entitlement hearing was scheduled for December 17 and 18, 2020. ECF No. 55.

Petitioners filed additional medical literature, a prehearing brief, and amended petition on October 22, 2020. Petitioners' Pre-Hearing Brief ("Pet. Pre-H Brief"), ECF No. 59; ECF Nos. 58, 60. The amended petition alleged that on December 16, 2013, A.E.S. was administered Pediarix (DTap/IPV/HepB), Hib, PCV13 and RotaTeq vaccinations from which she suffered injuries including "an on-Table encephalopathy which led to her death. In the alternative, the above vaccinations caused an Off-Table encephalopathy, pulmonary edema, visceral congestion, and death." Amended Petition at 1, ECF. No. 60.

On November 12, 2020, respondent filed his pre-hearing brief. Respondent's Pre-Hearing Brief ("Resp. Pre-H Brief"), ECF No. 61. On the same date, petitioners filed additional medical literature, medical literature summaries, and demonstrative exhibits. ECF Nos. 62-66. Respondent filed his medical literature summaries on November 19, 2020. ECF No. 69. The parties filed a joint pre-hearing submission on December 3, 2020. Joint Pre-Hearing Submission ("Joint Sub."), ECF No. 75.

A virtual hearing was held on December 17 and 18, 2020. During the hearing, Drs. Shuman and McCusker referenced additional literature which was ordered to be filed after the hearing. ECF

[3] In the interim, petitioners filed four unopposed motions for extensions of time to file expert reports, which were granted. ECF Nos. 18-22.

[4] In the interim, respondent filed two unopposed motions for extensions of time to file expert reports, which were granted. ECF Nos. 33-34.

No. 79. On February 1, 2021, petitioners filed their additional literature and respondent filed a supplemental report and the additional literature from Dr. McCusker. ECF Nos. 86-87.

The parties filed post-hearing briefs on May 3, 2021. Petitioners' Post-Hearing Brief ("Pet. Post-H Brief"), ECF No. 90; Respondent's Post-Hearing Brief ("Resp. Post-H Brief"), ECF No. 89.

This matter is now ripe for decision.

II. Overview of the Case

On December 16, 2013 at approximately 11:00 am, A.E.S. was administered Pediarix, Hib, PCV13, and Rotateq vaccinations at her two-month well-baby check-up. *See* Petition, ECF No. 1; Amended Petition, ECF No. 60. Between 5:45 and 6:15 pm, A.E.S. was found in her bassinet face up and barely breathing with a pale blue tint to her skin. En route to the hospital, A.E.S. stopped breathing. Despite resuscitation efforts, she was pronounced dead at approximately 7:15 pm. Petitioners allege that the vaccinations administered to A.E.S. caused her to suffer a Table encephalopathy leading to her death or, alternatively, a non-Table encephalopathy, pulmonary edema, visceral congestion, and death. Amended Petition at 1.

Respondent disagrees, arguing that the coroner concluded A.E.S. died of Sudden Unexplained Infant Death ("SUID") and vaccines are not implicated as a cause of SIDS/SUID. Resp. Post-H Brief at 3, 15-16. The medical examiner concluded that the cause of death was "undetermined" and the findings were consistent with SUID. Pet. Ex. 3 at 1,4.

The differential diagnosis of sudden death in infants can be challenging and complex. A distinction exists between sudden unexplained infant death ("SUID") and sudden infant death syndrome ("SIDS"). The two are not synonymous and the distinction will be further clarified below. Infants may die suddenly and unexpectedly for a variety of reasons, but a determination of SIDS can only be made after a thorough autopsy, death scene investigation, and review of the clinical history. Even after such due diligence, approximately 85% of SIDS cases remain unexplained, and the other 15% comprise a host of medical disorders, accidental and non-accidental trauma, and overlay. Pet. Ex. 55 at 3.[5] In 1989, SIDS was redefined by a panel convened by the National Institute of Child Health and Human Development as "[t]he sudden death of an infant under one year of age which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history." *Id*. SIDS is now defined as the sudden, *unexpected* death of an infant under the age of 1, usually during sleep, that remains unexplained after a thorough death scene investigation, including the performance of a complete autopsy and review of the circumstances of death and clinical history. *Id*. at 3-4 (emphasis added). Based on this definition, SIDS is a diagnosis of exclusion used when other possibilities have been ruled out. *Id*. at 4.

The parties agreed that the medical records and autopsy report are accurate, to the extent that they are consistent with petitioners' affidavits and hearing testimony. Joint Pre-Hearing

[5] POTTER'S PATHOLOGY OF THE FETUS, INFANT AND CHILD 841 (Enid Gilbert-Barness ed., 2nd ed. 2007), filed as "Pet. Ex. 55."

Submission ("Joint Sub.") at 1, ECF No. 75. The parties further agreed that, to the extent the affidavits and hearing testimony of the petitioners' conflict with the medical records or include information not covered in the medical records, the special master will need to determine which evidence is more credible or whether such additional evidence is credible. *Id*.

The parties dispute the significance of the autopsy findings, specifically the presence of cerebral edema. Joint Sub. at 1.

Petitioners initially presented multiple theories to satisfy *Althen* Prong I. However, at the time of the hearing, petitioners advised that "[t]he following theories are no longer to be considered by the Court: direct toxic insult from pertussis toxin, polysaccharide conjugates of pneumococcus, or Tween80; and maternal transmission of antibody." Pet. Post-H Brief at 14 n.2; Tr. at 172.

III. Issues to be Determined

a. Whether A.E.S. suffered a Table encephalopathy, as defined by the Qualifications and Aids to Interpretation ("QAI"), 42 C.F.R. § 100.3(b)(2)(i)(a) (effective July 23, 2015 to March 20, 2017), leading to her death.
b. Alternatively, if A.E.S. did not suffer a Table encephalopathy, whether petitioners have satisfied their burden under the three prongs of *Althen* for an off-Table encephalopathy and vaccine-related death.

IV. Factual Evidence

A. Affidavits and Testimony of Abigail Sims, Daniel Sims, and Rocky Kennedy

1. Affidavits and Testimony of Daniel Sims

Mr. Sims submitted two affidavits. *See* Pet. Ex. 8; Pet. Ex. 136. Mr. Sims is the biological father of A.E.S. The following are his affirmations: A.E.S. was a healthy infant, developing normally. Pet. Ex. 8 at 1-2. On December 16, 2013, he accompanied his wife to the pediatrician for A.E.S.'s well child appointment at which she received Pediarix, Hib, PCV13, and RotaTeq vaccines. *Id*. at 1.

Mr. Sims cared for A.E.S. that day after his wife went to work. Pet. Ex. 8 at 2. At about 5:00 pm, he fed and burped A.E.S. and laid her on her back in her bassinet to sleep. *Id.* When he checked on her around 5:45 pm, A.E.S. was not breathing and had a bluish tint to her upper lip. He picked her up, put her in the car, and drove to Baptist Memorial Hospital where his wife worked, calling Mrs. Sims from the car. *Id*.

The doctors in the emergency room worked on A.E.S. for about an hour but were unable to resuscitate her. She was pronounced dead at 7:15 pm. Pet. Ex. 8 at 2.

A.E.S.'s death had a profound impact on the family, forcing them to leave their apartment and get rid of all things that reminded them of her death. Pet. Ex. 8 at 2. About a year after A.E.S.

died, the Sims had another child. He and his wife often stayed up at night after their son received his vaccinations to make sure he did not stop breathing. *Id*. at 2-3.

In his second affidavit, Mr. Sims clarified that he went with his wife to the pediatrician's office for A.E.S.'s well child visit on December 16, 2013, but remained in the waiting room with their two sons. After A.E.S. received her shots, they went home. Pet. Ex. 136 at 1. A.E.S seemed tired after her vaccinations. *Id*.

At that time, Mr. Sims was a stay-at-home father. When they arrived home from the pediatrician's office, Mr. Sims held A.E.S. on the couch, then watched TV while his wife fed her. That afternoon, A.E.S. was "spaced out," and not cuddling or snuggling as usual. Pet. Ex. 136 at 2. Mr. Sims drove his wife to work. Upon returning home, he gave the boys a snack while they watched cartoons and A.E.S. napped. The boys then went to play in their room. A.E.S. was fussing, so he fed her again. *Id*. She fed less and a bit slower than usual. He placed her in her bassinet face up, neck neutral, arms at her side, and hands unclenched. He went back to the kitchen to wash the dishes. *Id*. There was no baby monitor, so he checked on her periodically as was their routine. When he returned after finishing the dishes, he found A.E.S. with slightly blue lips, turned onto her side with her head canted upward and tilted back a good bit with her mouth open. *Id*. She was pale, her eyes were closed, and one hand was clenched. Mr. Sims heard A.E.S. exhale as he picked her up. She was limp but still warm to the touch. He held her close to his chest, went to the living room to call his wife and get the boys dressed and into the car. *Id.* at 3. Mr. Sims thought he felt A.E.S. move twice in his arms in the four minutes it took him to get her and the boys into the car. It took six minutes to get to the hospital. Once at the ER, the doctors worked on A.E.S. for around an hour. She was pronounced dead at 7:15 pm. *Id.* at 3.

"Rocky the medical examiner" spoke to him and his wife at the hospital not long after A.E.S. died. Mr. Sims provided Rocky with the events of the afternoon, and Rocky made the diagrams contained in his written report. Pet. Ex. 136 at 3.

Mr. Sims testified at the hearing. He was 40 years old and worked for the facilities maintenance department at the University of Mississippi. Tr. 45-46. When A.E.S. was born, he was a stay-at-home dad homeschooling their two sons. Tr. 47. His wife worked at the hospital from 3:00 pm until anywhere between 7:00 pm and 11:00 pm, depending on what was going on the hospital floor where she worked. Tr. 49.

Mr. Sims stated his wife's pregnancy and birth of A.E.S. were without complication. Tr. 47. He described A.E.S. as alert, wide awake, always looking around, with a "presence on her face." She would fall asleep in your arms and sometimes cooed back when you spoke to her. Tr. 50. She was breastfed, so his wife would pump and leave bottles for him when she was at work. Tr. 50-51. A.E.S had no problem taking a bottle. Tr. 51.

Mr. Sims stated they lived in a two-bedroom apartment. His wife had a lot on her plate so he would get up early, get everything ready for the day, feed and dress the boys, and take care of the house. Tr. 51.

Mr. Sims did not notice anything unusual about A.E.S. on the morning of December 16, 2013. They all went to the pediatrician, and he stayed in the waiting room with the boys while his wife took A.E.S. to have her vaccines. Tr. 52-53. He was surprised that A.E.S. was very quiet when his wife came back out because the boys always came out in tears after shots. A.E.S. was quiet on the ride home. He held her on the couch while his wife got ready for work, and they all took his wife to work. Tr. 53.

After returning home, A.E.S. was quiet and tired. He recalled the boys being tired after getting shots, so he thought it was part of the side effects of her vaccines. Tr. 55. He sat on the couch with her for 30 to 40 minutes, fed her, and laid her down to nap. Tr. 55-57, 76. He described A.E.S. as "super spaced out"; not "locking on to any one person", but "just kind of looking up, just looking around the room" with her mouth more open than usual. She seemed "not all there." Tr. 59-60. She was quiet, not fussy. Tr. 77. He recalled it taking longer than normal for her to feed, like she was not interested, and she ate very slowly. Tr. 55-56, 77. She looked very tired, so he put her on her back in the bassinet, facing up, arms at her sides, legs straight. Tr. 57.

He then went to the kitchen to clean the dishes and check on the boys. About 20 minutes later, he went back to check on A.E.S. Tr. 58. They did not have a baby monitor, so he would check on her every 5-20 minutes to see if she was still asleep. Tr. 59-60. When he went in to check on her, "[H]er head was extended back. Her mouth was open. She was half onto her side. Her arms were slightly back. It looked like she was almost trying to turn onto her side slightly." Tr. 58, 61. Her head was ". . . facing upward in the bassinet with her mouth open, her eyes slightly closed. And her lips were blue at the ends." Tr. 62. When he picked her up, she made a noise "like exhaling", and he looked at her to see if she was going to make another noise then clutched her to his chest, grabbed the phone, and called his wife. As he was calling, he told the boys to get their shoes and coats on. Tr. 58-59, 63. She was limp and very, very pale. Tr. 62-63. He put A.E.S. in her car seat in the house. At that point, he thought she had already died. Tr. 63. They left the house heading to the hospital in less than four minutes. Tr. 59. He got to the hospital in under six minutes. His wife was waiting there, grabbed the car seat with A.E.S., and ran into the hospital. He parked the car and ran into the hospital carrying the boys. Tr. 64. His wife's coworkers took the boys, and he ran to where his wife was. Three or four doctors were there trying to revive A.E.S. She was pale and very limp. He held his wife until a doctor came over and told them A.E.S. was gone. Tr. 65-66. He later learned that she had respirations and a heartbeat when they arrived at the hospital. Tr. 63-64.

Mr. Sims did not recall much of the details after that, but they went to another room where Mr. Kennedy, who he had met a couple times at the hospital, came to talk to them. He tried to answer the questions as best as he could. Tr. 66-67. He confirmed the information contained in Mr. Kennedy's report but noted they did not have a baby monitor. Tr. 69-73; *see* Pet. Ex. 7 at 7-9. He was directed to the diagram on page 8. He told Mr. Kennedy that "[h]er head was extended back. Her mouth was open. Her eyes were slightly open. One arm was over the other. She had one leg that was slightly, like, cocked back, almost as if she was trying to roll to her side with her head extended back. Her mouth was open. And her face was, like, extremely pale." Tr. 73.

2. Affidavit and Testimony of Abigail Sims

Mrs. Sims submitted two affidavits. *See* Pet. Ex. 9; Pet. Ex. 135. She is A.E.S.'s biological mother. Mrs. Sims affirmed the following: prior to December 16, 2013, A.E.S. was a healthy baby. On December 16, 2013, she and Mr. Sims took A.E.S. to the pediatrician, where she was given Pediarix, Hib, PCV13, and RotaTeq vaccines. Pet. Ex. 9 at 1-2.

Mrs. Sims received a telephone call from Daniel while at work between 5:45 pm and 6:00 pm that he found A.E.S. in her bassinet, not breathing. He was on the way to the ER at the hospital where she worked. Once at the hospital, the doctors worked on A.E.S. for about an hour in the ER. A.E.S. was pronounced dead at 7:15 pm. Pet. Ex. 9 at 2.

Mrs. Sims was profoundly affected by the death of A.E.S. She and Mr. Sims stayed up at night taking turns holding their son, who was born a year later, after he received his vaccinations, unable to sleep out of fear he too would stop breathing. Pet. Ex. 9 at 2.

In her second affidavit, Mrs. Sims affirmed that she and her husband took A.E.S. to the doctor on December 16, 2013. A.E.S. was seen by a nurse, not a doctor, and given her shots; they were told she was growing wonderfully and was healthy and perfect. Pet. Ex. 135 at 1.

A.E.S. was breastfed on demand between 5-8 ounces per feeding, so Mrs. Sims pumped and left bottles while she was at work. A.E.S. would usually sleep for an hour or so after feeding. Pet. Ex. 135 at 2.

A.E.S. was a happy baby, who had just started cooing, smiling, and rolling over in the weeks prior to her death. Pet. Ex. 135 at 2.

After A.E.S. was given her shots, Mrs. Sims sat and fed her until she calmed down before leaving the doctor's office. At home, Mrs. Sims held her until she had to get ready for work at 3:00 pm. A.E.S. slept most of time, opened her eyes sometimes but was not making eye contact and had a distant look, as though she was looking past Mrs. Sims. She did not cuddle. Pet. Ex. 135 at 2.

Mrs. Sims put A.E.S. in her car seat in the house so she could get ready for work. Mr. Sims drove her to work with the children in the car. Pet. Ex. 135 at 2. Mr. Sims called her at work and said A.E.S.'s upper lip was blue, and he was bringing her to the ER. She met him downstairs and carried A.E.S. into the ER. A.E.S. was not breathing. Pet. Ex. 135 at 3. The ER doctors worked on A.E.S. for around an hour and pronounced her dead at 7:15 pm. "Rocky Kennedy the medical examiner" spoke to her and Mr. Sims in the ER after A.E.S. died. The family went home to Jackson, Mississippi afterward to stay with family until A.E.S.'s funeral. *Id*.

At hearing, Mrs. Sims stated she is a project manager for federal grants at the University of Mississippi School of Pharmacy. Tr. 9. She now has four boys, ages 12, 9, 5, and 10 months. A.E.S. was her third child, born between the 9-year-old and 5-year-old. Tr. 8. Mrs. Sims studied nursing but decided it was not for her and went into finance. She took CPR courses and worked at

two hospitals as administrative staff while she was in school. At the time of A.E.S.'s death, she was a floor secretary at Baptist Memorial Hospital North Mississippi. Tr. 9-10.

Mrs. Sims described her pregnancy, labor, and delivery as normal. A.E.S. was born without complications and was healthy thereafter with no illnesses. Tr. 11. At the time of A.E.S.'s death, Mrs. Sims was in school at the University of Mississippi from 8:00 am until about 1:00 pm and worked at the hospital from 3:00 pm to 11:00 pm. Finals had just ended, so things were more relaxed. Tr. 12. Mr. Sims took care of the children when she was in school and at work. A.E.S. was a happy baby and very connected to the family. Tr. 13. Mrs. Sims showed a picture of A.E.S. a few weeks before she died. Pet. Ex. 102.

A.E.S. was fed only breastmilk, every two to three hours or every four to five hours at night but was a frequent feeder. She would nap for about two hours at a time. Tr. 15. At the time of her death, she was smiling, cooing, and babbling and could roll from back to side to belly and from belly to side, but getting back on her back took some frustration. Tr. 16-17. She typically ate about four ounces, fell asleep while feeding, woke somewhat when burped, then drifted back to sleep. Tr. 16.

On the day A.E.S. died, the family awoke around 7:00 or 8:00 am. Mrs. Sims prepared breakfast for everyone; she always fed A.E.S. with the family. She breastfed about three times that morning before they left for the pediatrician. Tr. 14. They all went to the pediatrician, and Mr. Sims stayed in the waiting room with the boys while she went to the examining room with A.E.S. A.E.S. was examined by a nurse, noted as perfect, healthy, and on track in height and weight. She received the vaccinations in her thighs. A.E.S. cried, so Mrs. Sims nursed her to calm her before they all went home. Tr. 19-21. Mrs. Sims showed a picture of A.E.S taken by Mr. Sims at the pediatrician's office at around 12:00 or 12:15 pm, after her vaccinations. Tr. 39; *see* Pet. Ex. 103.

Once back home, Mrs. Sims held A.E.S. on the couch until she had to get ready for work at around 2:30 pm. She described A.E.S. that afternoon as sleepy, fussy, and looking really tired. She was not "looking at me" but "kind of looking past me" like she was daydreaming. She "was just needing me, so I just held her until I had to get ready" for work. She was feeding every 20 to 30 minutes but not really feeding, she was seeking comfort. Tr. 21-22. A.E.S. was normally a very happy baby who hardly cried, but that afternoon she was fussy, whining, whimpering and "had a quiet look in her eye." Tr. 21-22. When awake, she had a quiet whine, like she had a headache and didn't want to make noise. Tr. 40. Mrs. Sims walked with her and soothed her knowing she did not feel well after her shots. Tr. 23. She spit up but was not actively vomiting. Tr. 41.

The family had one car and did not have a babysitter, so they all took her to work, which was about seven minutes away, at around 2:50 pm. Tr. 24. When at work, Mr. Sims would text her but knew she was not allowed take calls until her break, so it was odd when he called that day. Tr. 25. Mrs. Sims went into a supply closet to take the call. Tr. 26. Mr. Sims was incoherent, saying he could not wake someone, then she realized it was A.E.S. She went to the head nurse while on the phone with her husband. The head nurse called down to the ER to alert them and said an ambulance would take 10 minutes to get to the Sims's apartment. Mrs. Sims told her husband to drive to the ER which would be faster. Mr. Sims called back from the car. Tr. 26-27. He was panicked driving and arrived within four or five minutes. Tr. 28. Mrs. Sims waited at the ER

entrance, grabbed the car seat from the car, and ran into the ER. Tr. 29. A.E.S. looked slightly grayish, her lips were blue, but she was still warm to the touch. The first doctor she saw pulled A.E.S. out of the car seat and turned her over, patting her back and looking for a pulse. She did not recall if there was a pulse, but A.E.S. was not breathing at that point. The doctor brought A.E.S. into a room where nurses and staff were waiting and started CPR, administering medications, and suctioning. Mrs. Sims was in her uniform, so she doesn't think they realized she was the mother. She stayed in the room the entire time until a doctor approached her and said there was nothing more they could do. Tr. 29-31.

Mrs. Sims knew Rocky Kennedy. He was always called for a death at the hospital, and she worked on a hospice and renal failure unit. Tr. 31. Mr. Kennedy spoke to her and Mr. Sims. They answered all his questions. She does not know if he went to their apartment, because they left the next day to stay with family in Jackson. A.E.S. was buried there. Tr. 33-34.

Both Mr. and Mrs. Sims described their apartment to Mr. Kennedy as a two-bedroom apartment where A.E.S. slept in a bassinet in their bedroom. Tr. 17, 34-35. They did not have a baby monitor as reflected on the form. Tr. 41. Mrs. Sims knew about SIDS and took precautions with all her children. A.E.S. was always placed on her back in her bassinet, with nothing in the bassinet except maybe a pacifier, which she was not fond of. They stopped swaddling her at around 3-4 weeks old because she didn't seem to like it. Tr. 17-19.

After A.E.S. died Mrs. Sims had another baby who was born at 37 and a half weeks and was very small. They were told he had Long QT syndrome, probably because he was not full-term. He was on a cardiac monitor for the first six months, which went off frequently when he cried because his heart rate would go up. Tr. 36-37. His EKG was normal at his pediatric cardiologist visit at one month old. The doctor told them that they don't know how many babies are born with Long QT syndrome because EKGs are not done on healthy babies when there is no history of SIDS in the family, so it may be more common than is known. Their son is fine now. Tr. 38.

3. Report and Testimony of Rocky Kennedy, CMEI

An investigation report was generated by Rocky Kennedy, CMEI, which included references to the ER record and the autopsy report. The report history included a 11-week-old who had a check-up and received vaccinations earlier in the day, with no reactions noted throughout the rest of the day until the stated incident. Pet. Ex. 7 at 1. A Sudden Unexplained Infant Death Investigation ("SUIDI") form was completed by Mr. Kennedy on December 16, 2013. Pet. Ex. 7 at 7-14. The form included a host of questions with answer options to be used during witness interviews, including but not limited to the medical history of both mother and baby during pregnancy, where the baby was found, how the baby was positioned both before and after being found, what the baby was wearing, the surrounding environment, resuscitation attempts, an incident scene investigation, a diagram of the baby when found, and a summary from the pathologist. Pet. Ex. 7 at 7-14. Mr. Kennedy's notes on the form included: blueness top lip, baby was pale, well baby, routine vaccinations received the morning of death, and that the "apartment is very clean and well kept." *Id.* at 9, 12. On a diagram, Mr. Kennedy wrote, "on back, slightly left lateral arms over the side; head/neck back/ slightly left". *Id.* at 13. A copy of the death certificate was attached. *Id.* at 15-16.

Mr. Kennedy testified at hearing. He is the county medical examiner investigator ("CMEI") for Lafayette County. Tr. 80-81. He has a bachelor's degree in business communications from Georgetown College in Kentucky, graduated from Mid-America College of Funeral Technology, and is licensed in funeral procedures in the State of Mississippi. He is certified as a county medical examiner investigator in Lafayette County to conduct death investigations as required by the elected coroners and appointed deputy coroners. He is also trained and certified through the Mississippi State Medical Examiner's office as a sudden unexplained death investigator. Tr. 81. If a death takes place in the hospital, he is called by the hospital. Otherwise, he is contacted by 911 in Lafayette County for all deaths occurring in the county. Tr. 82. He has been in this position since 2009. He previously worked in a funeral home as a licensed funeral director and embalmer, and he was also deputy coroner to the previous medical examiner in Oxford. Tr. 83. He investigates about 48 to 50 deaths a month, but much more during the pandemic. Tr. 84.

Mr. Kennedy knew Mrs. Sims from the hospital and was impressed by her working to put herself through school while still being home with her children during the day. He would not ever forget the emotions he saw Mr. and Mrs. Sims go through when A.E.S. died. Tr. 84.

Mr. Kennedy was already at the hospital investigating another death when A.E.S. died. Tr. 84. He gives the same attention to all deaths, but his questions are different for an unexplained infant death. Tr. 85.

Mr. Kennedy confirmed Petitioner's Exhibit 7 was his report. Tr. 85. He printed the form on the morning of December 17, 2013, which is why that date is reflected. Tr. 86. He issued a permit requesting that the State Medical Examiner complete a post-mortem examination. At that time, autopsies were conducted in Jackson, Mississippi, but now the Medical Examiner's Office and Mississippi Crime Lab are in Pearl, Mississippi. Tr. 87. He prepared the SUIDI Reporting Form. Tr. 88; Pet. Ex. 7 at 7. The information on the form came from interviewing the petitioners in the emergency room and from a follow-up phone call. Tr. 88-89. Mr. Sims provided the information about A.E.S.'s positioning as contained in box 18 of the form. *See* Pet. Ex. 7 at 8. Mr. Sims did not use the word "hyperextended"; that word is contained on the standard form. Mr. Sims said her head was back and to the left. Tr. 90-91. He uses a doll or stuffed animal to help the parents give information. Tr. 91, 97. The child was not wedged between two things. Tr. 92-93; Pet. Ex. 7 at 8. Mr. Kennedy manually inputs the information he receives from the interviews into the online case reporting system. Based on information from Mr. Sims, box 31 includes "blue present on top lip", and box 32 includes "limp, flexible." Tr. 93; Pet. Ex. 7 at 9. The information on page 9 about A.E.S.'s medical history and vaccines the morning of December 16, 2013 came from his interview with the parents. The list of vaccines came from the Children's Clinic of Oxford and was entered later. Tr. 94. The information on page 10 came from the parents, the medical records at Baptist Hospital, and the care provider. Tr. 94; Pet. Ex. 7 at 10. The information that A.E.S. took six ounces of breast milk came from Mr. Sims who fed her last and Ms. Sims who said that the bottles normally contained six ounces. Tr. 95; Pet. Ex. 7 at 10.

Mr. Kennedy did not recall going to the Sims's home, although the notation that the "apartment was very clean and well kept" suggests that he did. Tr. 91, 96-97; Pet Ex 7 at 12.

Mr. Kennedy stated that Mr. and Mrs. Sims were very forthcoming when he questioned them, with no inconsistencies which he noted on the form. He referred them to grief counseling. Mr. Sims provided the information for the body diagram. Tr. 98-99. All the check marks were based on information from the parents. There was no trauma, injury, poisoning, or intoxication. Tr. 99. He did not know why the boxes for asphyxia, environmental hazards, or preterminal resuscitative treatment were not marked off, but there were no signs of that seen. Tr. 100. The information that A.E.S. had received immunizations that day with no reaction until the incident was provided by her parents. Tr. 100.

B. Medical History

1. Medical History Prior to the December 16, 2013 Vaccinations

A.E.S. was born on October 1, 2013, following an uneventful pregnancy and birth. Pet. Ex. 1 at 1; Pet. Ex. 5 at 82; Pet. Ex. 6 at 99; *see generally* Pet. Ex. 4. Mrs. Sims was 24 years old during her pregnancy with A.E.S. On September 6, 2013, Mrs. Sims was administered a Tdap vaccine as part of her routine prenatal visit. Pet. Ex. 6 at 21.

A.E.S was petitioners' third child, joining two older brothers. Pet. Ex. 2 at 6. A.E.S. weighed 6 pounds, 11 ounces at birth with Apgar scores[6] of 9 and 9. Pet. Ex. 6 at 99.

A.E.S. was a well, breastfed child with no concerns in the first two months of life. Pet. Ex. 2 at 8-10.

2. Medical History Following the December 16, 2013 Vaccinations

A.E.S. was presented for a well-baby check at approximately 11 weeks old on December 16, 2013 at around 11:00 am. Pet. Ex. 2 at 16-17; Pet. Ex. 7 at 9. She was meeting all milestones for her age: she followed with her eyes to midline, awoke to loud noise, responded to sound, lifted her chest when prone, kept her head steady when in a sitting position, spontaneously smiled, and interacted with her mother. Pet. Ex. 2 at 16. Physical examination was normal. *Id*. at 18. She was administered Pediarix, Hib, PCV13 and RotaTeq vaccinations. *Id.* at 7; 18-19.

At approximately 6:34 p.m., A.E.S. arrived at Baptist Memorial Hospital in an infant carrier via private vehicle. She was pale. Mr. Sims reported that A.E.S. stopped breathing eight minutes prior to arrival. A nurse removed her from the carrier and carried her to a trauma room. She had no pulse. Pet. Ex. 5 at 10-12, 58. CPR was started, she was intubated and given epinephrine. *Id.* at 58. Her temperature was 96 degrees. *Id*. at 10-12; 57-58. Respiratory arrest, cardiac arrest, and cyanosis were documented. Pet. Ex. 5 at 6. The record includes "gross pulmonary edema from trachea." Initial cardiac rhythm was "asystole." Cardiac arrest and sepsis were circled in the "DDX" section of the form, with anaphylaxis written in. *Id*. at 11. The History of Present Illness documented a "normal day – shots – ate normally." *Id.* at 10; Pet. Ex. 7 at 1. Mr. Sims reported giving A.E.S. a bottle, burping her, and putting her into her bassinet to sleep at

[6] The Apgar score is "a numerical expression of the condition of a newborn infant, usually determined at 60 seconds after birth, being the sum of points gained on assessment of the heart rate, respiratory effort, muscle tone, reflex irritability, and color." *Apgar score*, DORLAND'S ILLUSTRATED MEDICAL DICTIONARY 1654 (33rd ed. 2019) [hereinafter "DORLAND'S"].

approximately 5:30 pm. Pet. Ex. 7 at 7. When Mr. Sims checked on A.E.S. at approximately 6:15 pm, she was struggling to breath, her lips were blue, and she was pale. *Id*. at 1, 7. All attempts at resuscitation failed, and A.E.S. was pronounced dead at 7:15 pm. Pet. Ex. 5 at 11, 57-58.

3. Autopsy Report

Dr. Erin Barnhart of the Mississippi State Medical Examiner's Office for Lafayette County performed the autopsy. Pet. Ex. 3. She noted an 11-week-old who died on December 16, 2012 [sic].[7] General findings on autopsy included thymic, epicardial, and pleural petechiae[8], pulmonary edema[9], and visceral congestion. The cause and manner of death were "undetermined." Pet. Ex. 3 at 1.

Autopsy findings were generally unremarkable, except for a brain weight of 595 grams.[10] Pet. Ex. 3 at 3. Microscopic descriptions included vascular congestion[11] of the heart, intra-alveolar edema and congestion of the lungs, congestion and focal intraparenchymal blood in the thymus, and congestion of the liver, pancreas, spleen, and kidney. *Id*. at 3-4.

Dr. Barnhart documented a normal breast-fed baby who received her 12-week vaccinations that morning, was fed, burped, and placed on her back in a bassinette to sleep. She was found approximately 45 minutes later by her father, pale with blue discoloration of the upper lip. Pet. Ex. 3 at 4. She was taken to the ER and attempts at resuscitation were unsuccessful. There were no congenital abnormalities or acute injuries, toxicology was negative, and the histology was consistent with gross findings. *Id.* Dr. Barnhart concluded that the cause and manner of death were best classified as undetermined, with findings consistent with Sudden Unexpected Infant Death (SUID). Pet. Ex. 3 at 4.

VI. The Medical Experts

At the time of the hearing, petitioners pursued only the claims raised in their amended petition which included "an on-Table encephalopathy…" or, in the alternative "an off-Table encephalopathy, pulmonary edema, visceral congestion, and death" as a result of the Pediarix (DTap/IPV/HepB), Hib, PCV13, and RotaTeq vaccinations A.E.S. received on December 16, 2013. Amended Petition at 1, ECF No. 60; Pet. Post-H Brief at 14 n.2.

The four experts involved in this case are well known to the Court, equally impressive in their respective specialties, and all recognized as experts in their respective fields.

This is not a SIDS/SUID case as more fully set forth below and agreed upon by the respective pathologists, Drs. Shuman and Harris.

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[7] The autopsy is incorrect. The year of A.E.S.'s death and the subsequent autopsy should be 2013.
[8] Petechiae are pinpoint, non-raised, perfectly round, purplish red spots caused by intradermal or submucous hemorrhage. *Petechia*, DORLAND'S 1401.
[9] Edema is "the presence of abnormally large amounts of fluid in the intracellular tissue spaces of the body, usually referring to subcutaneous tissues." *Edema*, DORLAND'S 587.
[10] The expected range for brain weight was 461-555 grams. Pet. Ex. 3 at 3.
[11] Congestion is the excessive or abnormal accumulation of fluid, as of blood in a part. *Congestion*, DORLAND'S 398.

Accordingly, only those expert opinions regarding an on-Table encephalopathy or, alternatively, an off-Table encephalopathy and vaccine-related death, will be included in this decision.

A. Petitioners' Expert, Dr. Robert Shuman

1. Qualifications

Dr. Shuman graduated from Cornell University School of Arts and Sciences in 1963 with a degree in experimental psychology. He received his medical degree from Stanford University School of Medicine in 1968. Pet. Ex. 17 at 1. Dr. Shuman is board certified in pathology (neuropathology), neuroimaging, and neurology with a special competence in child neurology. *Id*. at 2. Dr. Shuman was in private practice at Child Neurology, Inc. from 1991-2006. *Id*. Dr. Shuman describes himself as a "pediatric neurobiologist," which he defines as a person who spends their life studying the development of children, their aberrations, the treatment for those aberrations, and prevention. Tr. 103. Dr. Shuman retired from private practice in 2006 and has not seen patients in a clinical setting since. Tr. 167-68. He now derives part of his income from litigation consulting and has been involved in many cases over the years, including about 11 vaccine cases since 2000. Tr. 125. When asked, Dr. Shuman did not believe he has had more than three cases, excluding Program cases, involving fatalities or reviewing autopsy reports. However, he has friends who are in pathology and they talk, he maintains his memberships in the American Academy of Pathology and in Neurology, he reads daily about neurology and pathology, and he maintains his board certifications. Tr. 169-70. He does not have any specialized training in immunology or toxicology but is interested in the principles of toxicology and developmental metabolism as it relates to toxicology. The papers related to neurotoxicology contained in his CV are from the 1970s. Tr. 170.

2. Opinion

Dr. Shuman issued two reports in this case and testified at hearing. Pet. Ex. 16; Pet. Ex. 92.

a. Dr. Shuman's First Report

In his first report, Dr. Shuman opined that the vaccines received by A.E.S. on December 16, 2013 caused her death by encephalopathy, cerebral edema, brainstem herniation, and cardiopulmonary failure hours later. Pet. Ex. 16 at 36.

Dr. Shuman noted a normal medical history and a healthy baby who received routine vaccinations just before noon on December 16, 2013 and was found clinically dead later that day. Pet. Ex. 16 at 16, 18. In the ER, "[D]uring resuscitation, her lungs became increasingly difficult to ventilate, produced increasing amounts of frothy edema…obtainable blood pressures progressively worsened" and she was pronounced dead 7+ hours after her vaccinations. *Id.* at 16. "This course of progressively worsening collapse of the cardiopulmonary system is atypical for SIDS" and A.E.S. did not die of SIDS. *Id.* at 16, 26.

Dr. Shuman defined SIDS as "[t]he sudden death of an infant under one year of age which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history." Pet Ex. 16 at 26.

According to Dr. Shuman, A.E.S. had no risk factors associated with SIDS. Pet. Ex. 16 at 24. She had no brain abnormalities, a normal birth weight, was growing normally in weight, length, and head circumference, no evidence of infection post-mortem, and was in a safe sleeping environment on her back on a hard surface with no bed clothes to entangle her. *Id*. SIDS is less common in girls, and A.E.S. was born full-term with no epidemiological or environmental risk factors for or family history of SIDS. *Id.*

Dr. Shuman discussed the vaccines A.E.S. received which included the Pediarix vaccine containing diphtheria, tetanus, and acellular pertussis (DTaP), recombinant hepatitis B, and inactivated polioviruses 1, 2, and 3; Hib vaccine; Prevnar 13 vaccine containing 13 antigens of pneumococcal conjugate; and Rotateq rotavirus vaccine, administered orally. Pet. Ex. 16 at 18. In total, she received ten vaccines in four different preparations with three adjuvants in three separate injection sites, which "constitutes a profound immunologic challenge." *Id*.

Dr. Shuman noted that the current DTaP contains three acellular pertussis antigens rather than the 3000 antigens previously contained in the whole cell DTP. The change to acellular pertussis was made in hopes that the acellular pertussis toxin would be less toxic while retaining immunogenicity. Pet. Ex. 16 at 19.[12] Citing *Steinman*, Dr. Shuman explained that the pertussis toxin in DTaP targets the brain producing hypotonic spells, systemic and neurologic collapse, coma, and seizures. Pet. Ex. 16 at 28; Pet. Ex. 62.[13]

Dr. Shuman discussed the Prevnar 13 vaccine as containing 13 polysaccharide antigens of 13 pneumococcal variants, with the antibodies produced equaling only half the mass of the antigen provoking it, but still qualitatively significant in an infant. Pet. Ex. 16 at 20. He provided the data following administration of Prevnar 13 vaccines at two, four, and six months of age and the statistics associated with SIDS, inferring that the closer one is to a notable event, the more likely it is that the notable event caused the result. Fifty percent of deaths occurred within 24 hours of vaccination, which is worthy of investigation. *Id*. at 23-24.

Dr. Shuman noted that the package insert for Prevnar 13 includes apnea observed in premature infants.[14] Pet. Ex. 16 at 21. He added that the pneumococcal polysaccharides in the Prevnar 13 are not as toxic as pertussis toxin, but the package insert shows they have been linked to cardiac mediated-cyanosis, vascular (cardiac)-mediated pallor, respiratory-mediated apnea, and nervous system-mediated hypotonia. *Id*. at 28. Table 4 of the package insert shows that of infants

[12] This literature supports a reduction of adverse events believed to have stemmed from the increased reactogenicity of the 3000 different proteins contained in the whole cell pertussis vaccine versus 2-5 proteins contained in the acellular pertussis vaccine. Further, the whole cell pertussis vaccine also contains neurotoxins, including endotoxin, pertussis toxin, and adenylate cyclase. Pet. Ex. 34 at 1.

[13] Lawrence Steinman et al., *Pertussis toxin is required for pertussis vaccine encephalopathy*, 82 PROC. NATL. ACAD. SCI. USA 8733 (1985), filed as "Pet. Ex. 62."

[14] The Prevnar 13 insert notes that the data is insufficient to assess the effects of concomitant administration of Prevnar 13 with HPV, MCV4, tetanus toxoid, and Tdap. Prevnar 13 is a conjugate vaccine containing Diphtheria CRM protein. Pet. Ex. 35 at 24.

two to 12 months of age vaccinated with Prevnar 13, 80% suffer irritability, 70% slept too much, and 50% had diminished appetite. Pet. Ex. 16 at 28; Pet. Ex. 35[15] at 9. According to Dr. Shuman, these "misbehaviors" show disrupted brain function in infants because "[t]he CNS of the younger infant is most susceptible to neural toxicity." Pet. Ex. 16 at 28.

Dr. Shuman discussed the autopsy findings as inconsistent with SIDS. There were no findings of chronic stress such as cellular infiltrates in organs or evidence of chronic immune stimulation in the thymus or spleen. Pet. Ex. 16 at 28-29. He explained that in normal infants, fetal hemoglobin (HgbF) diminishes and converts to adult hemoglobin (HgbA), but in SIDS babies chronic hypoxic stress stimulates the synthesis of HgbF and impedes the shift to HgbA, chronically impairing respirations. *Id*. at 27. Chronic stress in SIDS babies is also seen in the persistence of or regression to fetal fat from paravertebral fat. Pet. Ex. 16 at 29. Further, there was no extramedullary hematopoiesis[16] present in the liver, kidney, and spleen which also suggests chronic stress, chronic hypoxemia, or SIDS when present. A.E.S.'s heart was normal, with no signs of cardiomyopathy or chronic adrenergic stress. The lungs were congested consistent with "acute, severe, clinically apparent congestive heart failure and pulmonary edema." *Id*. Histologically, the thymus showed deep medullary bleeding consistent with severe congestive heart failure but no subserosal petechia, which are more superficial but may occur in SIDS. *Id.* at 30. The lungs were heavy at 120 grams, affirming the clinical impression of persistent, progressive pulmonary edema with increasing stiffness of the lungs, causing difficulty in ventilating during CPR. *Id*. The ER record documented frothy edema from her airway during CPR, further affirming the histopathologic findings of proteinaceous fluid in the bronchioles and the congestion of the alveolar capillaries. Succinctly, there were no signs of chronic stress of the organs indicative of SIDS. *Id*. at 31.

Further, A.E.S.'s brain weight of 595 grams was consistent with cerebral edema. Pet. Ex. 16 at 31. Dr. Shuman explained that when the brain swells, it pushes down on the brainstem, the more it pushes, the more the brainstem is compressed and the greater the compromise of normal brain function. *Id*. at 27. The hallmarks of the compression of the brainstem from edema include uncal[17] grooving, coning of the cerebellar tonsils, and caudal displacement of the medulla into the foramen magnum. He conceded none of these findings were documented by the medical examiner in this case because when the skull cap is removed "the squeezing, distorting, rostral-caudal pile-driving nature of the cerebral edema on the brainstem and cerebellum are lost once the tough fibrous constraints of the dura are released" and the brain flows back into its premorbid shape. Pet. Ex. 16 at 31. Here, the brain was heavy due to edema with increased prominence of the perivascular and pericellular spaces around neurons of their satellite cells, and of the oligodendroglia along the fiber tracts. There were rare, mild, and scattered early acute ischemic cell changes in the brain consistent with rapid death. There was no reactive or chronic gliosis, no evidence of chronic hypoxemia, and no evidence of chronic disease. *Id*.

Dr. Shuman argued that the findings of cerebral edema, pulmonary edema, and congestive heart failure are not features of SIDS. As stated above, findings of SIDS include petechial

[15] *PREVNAR 13 Highlights of Prescribing Information*, Pfizer (2016), filed as "Pet. Ex. 35."
[16] Hematopoiesis is the formation and development of blood cells. *Hematopoeisis*, DORLAND'S 823.
[17] Uncal is "of or pertaining to the uncus." *Uncal*, DORLAND'S 1970. The uncus is "the medially curved anterior end of the parahippocampal gyrus." *Uncus*, DORLAND'S 1971.

hemorrhages in the conjunctivae, pleura, and thymus, thymic atrophy, fetal fat, adrenal stress, or extramedullary hematopoiesis, none of which were present here. Pet. Ex. 16 at 36.

In Dr. Shuman's opinion, the DTaP and/or Prevnar 13 vaccinations received on December 16, 2013 caused encephalopathy and cerebral edema, which pushed down on and caused brainstem herniation affecting respiration and causing cardiopulmonary failure resulting in death hours after the vaccinations. The evolution of the encephalopathy between vaccination and death is unknown but not uncommon in a very young, non-verbal infant with no behavioral repertoire to express distress. Pet. Ex. 16 at 36. Once the cerebral edema caused axial herniation and the brainstem was impaired, death ensued soon after. A.E.S. "was not resuscitable because the brainstem could not resume control of the viscera." *Id.* She suffered multiorgan failure rapidly thereafter, and the occurrence of her encephalopathy within 72 hours of vaccination constitutes a "table" encephalopathy. *Id.* at 36-37.

b. Dr. Shuman's Supplemental Report

In his supplemental report, Dr. Shuman noted Dr. Harris's agreement that the brain weight on autopsy was heavy. Dr. Shuman referred to the brain weight as a "robust sign of cerebral edema" citing data from *Kayser*, *Shulz*, and *Coppoletta*, each from different times in history but all defining A.E.S.'s brain as unusually heavy and exceeding the mean weight for a female child by more than two standard deviations. In the absence of malformation, such heaviness is objective evidence of cerebral edema. Pet. Ex. 92 at 1-2; Pet. Ex. 47[18]; Pet. Ex. 48[19]; Pet. Ex. 49.[20] Dr. Shuman added that the younger the baby, the smaller the behavioral repertoire to display autonomic impairment: "[y]oung infants don't cry loudly about their distress. They die quietly." *Id.* at 3.

Dr. Shuman explained how the vaccines A.E.S. received can affect the brain. He submitted that although term infants are born with intact and functioning blood brain barriers ("BBB"), toxic/inflammatory environments can break down the BBB via destructive immunological processes. Pet. Ex. 92 at 3-4. Vaccines elicit cytokines necessary for inducing an immunological response. DTaP, Hib, and PCV vaccines are proven to stimulate the production and circulation of proinflammatory cytokines including interleukins ("IL") -1β (beta) and IL-6, tissue necrosis factor alpha ("TNF-α"), and granulocyte colony stimulating factor ("G-CSF"):

> IL-1β stimulates macrophage production, T-cell production and fever. IL-6 stimulates T and B cells and produces acute phase reactions such as [inflammation] and fever in the host. TNF-α stimulates formed macrophages to make more cytokines (in a positive feedback loop), stimulates inflammatory invasion by monocytes which then transform into more macrophages, and 'activates' endothelial cells.

[18] Klaus Kayser et al., *Height and Weight in Human Beings: Autopsy Report* 9-123 (Munich University of Applied Sciences 1987), filed as "Pet. Ex. 47."
[19] Dale M. Schulz et al., *Weights of Organs of Fetuses and Infants*, 74 ARCHIVES OF PATHOLOGY 244 (1962), filed as "Pet. Ex. 48."
[20] Joseph M. Coppoletta & S.B. Wolbach, *Body Length and Organ Weights of Infants and Children*, 9 AM. J. PATHOLOGY 55 (1933), filed as "Pet. Ex. 49."

Pet. Ex. 92 at 4. This increases vascular permeability and can cause separation of the endothelial cell lining of the blood vessel walls, leading to leaking of fluid and protein resulting in accumulation in the tissue causing swelling or edema. *Id*. The changes to the endothelium from inflammation is known as endothelial activation, and TNF-α is a potent cytokine activator of endothelial cells. *Id*. at 5. G-CSF stimulates the development and maturation of granulocytes that, when mature, cluster to ensure tissue lysis and necrosis at the site where they collect and degranulate. *Id*.

Dr. Shuman cited *Kashiwagi* to show that the production of the IL-1β cytokine is provoked more during the first year of life than later in life and more significantly by multiple vaccines rather than by a single vaccine. Pet. Ex. 92 at 5; Pet. Ex. 65.[21] *Kashiwagi* only provided age-related data for IL-1β and not IL-6, TNF-α, or G-CSF, but showed markedly increased circulating cytokines in those with fever. Circulating levels of potentially damaging cytokines was also seen in data from the H1N1 flu pandemic in 2009, which showed markedly increased serology levels of four cytokines in infants hospitalized with H1N1 flu when compared with those less sick, not hospitalized infants with the flu. Pet. Ex. 92 at 5.

Thus, *Kashiwagi* demonstrated both: an increase in cytokine production with an increased number of vaccines and an increase in cytokine production in those under the age of one. Pet. Ex. 92 at 5. Here, A.E.S. received multiple vaccinations containing numerous antigens intramuscularly and the RotaTeq vaccine orally. The vaccines generated cytokines that circulated to A.E.S.'s brain, disrupted the BBB, produced severe rapid cerebral edema, and caused A.E.S.'s death by axial herniation. *Id.* A.E.S. suffered a malignant form of cerebral edema which was widespread, rapidly progressive, and lethal within 6-8 hours after vaccination. *Id*. at 4.

c. Dr. Shuman's Testimony

Dr. Shuman defined encephalopathy as a disturbance of the brain, or abnormal or depressed expression of brain function: "…broadly speaking, an encephalopathy is a deviation, a depressive deviation, a negative deviation of behavior from that expected of that person." Tr. 127-28. Behaviors associated with encephalopathy are age dependent and different in infants, children, and adults. Tr. 128. He referenced the American College of Obstetrics and Gynecology as stating it is well-established that encephalopathy is a depression in the expected functions of an infant at that stage of development. Tr. 128-29.

Dr. Shuman stated that the autopsy findings showed objective signs of cerebral edema: a full and flattened brain "obviously under pressure," brain weight at least two standard deviations above the mean for a 10-week-old female, and the absence of inflammation or other obvious cause of death in the limited samples of the brain taken. Tr. 133-40, 142. He stated that encephalopathy is a dysfunction of brain tissue. As the brain swells, it takes up more space and the pressure within the skull increases. The brain is somewhat like fluid and when the volume and pressure increase, the brain shifts and cuts off vessels between the compartments. The pressure pushes downward on the brainstem, which causes bradycardia and interferes with functions such as focus, gaze,

[21] Yasuyo Kashiwagi et al., *Production of inflammatory cytokines in response to diphtheria-pertussis-tetanus (DPT), haemophilus influenzae type b (Hib), and 7-valent pneumococcal (PCV7) vaccines*, 10 HUMAN VACCINES & IMMUNOTHERAPIES 677 (2014), filed as "Pet. Ex. 65" and "Resp. Ex. E, Tab 4."

tracking, sucking, and swallowing. Tr. 134-36. The fontanelle of the newborn skull does not protect against mass expansion. The dura is fibrous and inelastic and does not give way, though the bone plates do move a little bit under the pressure. Tr. 133-34. The brain edema that was present shows the pressure the brain was under with its appearance on autopsy being flattened and smooth rather than corrugated and folded nicely with the sulci effaced, which is the external expression of cerebral edema. Tr. 137. Cerebral edema and heaviness were the only abnormal findings in her brain. Tr. 173, 138-39. Dr. Shuman conceded the brain examination was quite limited and it was uncertain what may have been missed by the pathologist. Tr. 137-40.

Dr. Shuman cited *Von Kries* to show how cytokines generated by vaccination can induce cerebral edema. Tr. 146; Pet. Ex. 144.[22] In *Von Kries* the European Union's FDA withdrew a Pediarix equivalent vaccine manufactured by Sanofi Pasteur from the European market after three children died. Tr. 146; Pet Ex. 144. The study compared the incidence of sudden unexpected death in age-determined groups of children who had been exposed to a vaccine in the preceding seven to ten days and those who had not. All the children were autopsied. The three who died after vaccination were a 12-month-old found dead in his bed two days after vaccination; a 17-month-old found dead in her crib less than 24 hours after vaccination; and a 22-month-old found dead within 24 hours of vaccination. All received the hexavalent vaccine, died unobserved, and had cerebral edema on autopsy; none had inflammatory cell infiltrates indicative of SIDS. Tr. 148-49. All three cases are similar to A.E.S. following the hexavalent vaccine. Tr. 150. Dr. Shuman agreed *Von Kries* did not find proof of causal relationship between the vaccination and death. Tr. 174.

Dr. Shuman discussed *Traversa*, a study filed by respondent, to show that the first immunizations at two months of age have more adverse reactions than subsequent vaccinations at four and six months old because two months olds are more fragile. Tr. 152-53. The *Traversa* study concluded that the highest relative risk was within seven days of the first vaccine dose, which is administered when the risk of sudden unexpected death is greater. Tr. at 156-57; Resp. Ex. A, Tab 16 at 9. Dr. Shuman pointed to Table 5 of *Traversa* to show a risk increase of almost three times with hexavalent vaccines like A.E.S. received. Tr. 157-59; Resp. Ex. A, Tab 16 at 8. *Traversa* included a different vaccine with different adjuvants from a different manufacturer than the one used in *Von Kries*. Tr. 152-54; Resp. Ex. A, Tab 16[23] at 9. In Dr. Shuman's opinion, *Traversa* validated the findings of *Von Kries* and other articles that were not submitted. Tr. 174-75.

Dr. Shuman added that A.E.S.'s thighs showed swelling at the injection sites on the autopsy photographs, an indication of an inflammatory reaction of the local tissue, which should occur for cytokine release by circulation. Tr. 161; Pet. Ex. 18 at 2. He added that the vascular system is very reactive to cytokines and the cytokines released by adjuvanted vaccinations, which include IL-1, IL-6, tumor necrosis factor, C55 complement, and some prostaglandins, are extraordinarily and systemically vasoreactive on the brain and pulmonary vasculatures showing their effects by producing cerebral and pulmonary edema, third-spacing, hypovolemic hypotension, shock, and progressive encephalopathic death as seen with A.E.S. Tr. 162-63.

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[22] Rüdiger von Kries et al., *Sudden and unexpected deaths after the administration of hexavalent vaccines (diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, Haemophilius influenzae type b): is there a signal?*, 164 EUR. J. PEDIATRICS 61 (2004), filed as "Pet. Ex. 144."

[23] Giuseppe Traversa et al., *Sudden Unexpected Deaths and Vaccinations during the First Two Years of Life in Italy: A Case Series Study*, 6 PLOS ONE e16363 (2011), filed as "Resp. Ex. A, Tab 16."

Dr. Shuman disagreed with Dr. McCusker that the congestion of the organs and the frothing of the lungs was from resuscitation efforts. He stated the frothing was indicative of the edema fluid transmuting across vasculature in the pulmonary space. The frothing was the pulmonary edema fluid bubbling up through the tracheobronchial tree and was part of the third-spacing. The same thing that occurred in the pulmonary vasculature occurred in the brain vasculature, producing cerebral edema. "…[S]he was third-spacing peripherally, she was third-spacing pulmonarally, she was third-spacing in the head, and she was, as a result, becoming hypovolemic and hypotensive." This was all related to the process of the cytokines. Tr. 175-77. He was not suggesting that the release of cytokines from the vaccinations caused the brain edema by direct toxic insult and deferred to Dr. Gershwin for further explanation. Tr. 172.

Dr. Shuman stated that basic knowledge of the repertoire of infant behaviors is necessary to determine if an infant is suffering an encephalopathy. Tr. 129. Two-month-olds are expected to be able to maintain body temperature, blood pressure, and respiration, roll up and cuddle in your arms, fall into you, and turn toward you to nestle like a newborn. They can focus on you, smile responsively when you are within their gaze and track you for a little bit. They should reach toward an object but not necessarily grasp it, more like a push forward. They should begin to develop head control, so when pulled up to sit they help by bringing the head in the midline of the body. Resting tone should be in flexion. They begin to roll at two months from front to back and back to front. Tr. 129-31. The focus here would be on A.E.S.'s visual gaze, fixation and feeding behavior, specifically if she was able to root if she fed well before. It was unclear whether A.E.S. was rooting, able to suck, or if she withdrew milk on the afternoon of her death. Tr. 131.

Relying on the parents' observations, Dr. Shuman determined that A.E.S. was encephalopathic, displaying an altered mental state for a two-month-old child: she was irritable, unable to self-soothe, did not feed well, and did not have normal gaze or social response. Tr. 140-41. The father described her as "less cuddleable" and cuddling is a baby's adaptive response to touch. Tr 143-44. The mother described a "quiet look in her eye" which was a lack of visual focus and engagement, a primary infant ability. Tr. 144. The mother described her as not really being there and not responding, indicating a lack of emotional responsivity, which is the basis of emotional bonding between mother and baby that starts at birth and broadens in the behavioral repertoire. Tr. 144. Further, the mother described her appearing to have a headache. An infant cannot point to pain but can express discomfort, and her mother described comforting her and responding to her persistent distress. Tr. 145-46. When discovered in her bassinet, A.E.S. was in hyperextension with her arms extended, which is a decerebrate posture and a sign of axial herniation and encephalopathy. Tr. 140. Dr. Shuman was confused by the father reporting that she drank a bottle, because the autopsy showed only "a trace of mucoid food in the stomach". Tr. 136-37. In Dr. Shuman's opinion, A.E.S. was in the process of encephalic encephalopathy which completed between the time the mother went to work and before the father found her. Tr. 141-42. Encephalopathy also requires a clinical diagnosis, and he relied on the parents' testimony for the necessary clinical information. There was nothing in the medical records that described the clinical signs necessary to make a diagnosis. Tr. 171.

Based on the evidence, Dr. Shuman concluded that A.E.S. was encephalopathic with a decreased level of consciousness indicated by decreased or absent responses to her environment, clinical signs of absent eye contact, and absent or inconsistent responses to external stimuli, which

correlated with significant progressive cerebral edema and axial gradation and compression of function of the brain tissue. Tr. 163. This resulted from a biologically fragile two-month-old receiving 23 antigens by injection in her thighs and the rotavirus vaccine by mouth. Tr. 150-51; 159. The vaccines contained cytotoxic compounds to make them more antigenic and was an overwhelming antigen exposure at a fragile age of development. As a result, she was "found dead with subtle signs of compressive encephalopathic disturbance manifested by changes in mood, soothing, sucking, cuddling and gaze." Tr. 160. The PCV13 and Pediarix vaccines warn about apnea and bradycardia with arrest requiring resuscitation in premature infants. This includes infants born between 26- and 36-weeks gestational age who remained in the neonatal ICU for eight to 16 weeks postnatal age and were vaccinated during that time, with as many as 15% having apneas, bradycardias, and diminished cardiopulmonary function. These babies were monitored, but some still needed resuscitation. This shows how vulnerable younger infants are to toxins as supported by the *Von Kries* study and explains what led to the encephalopathy that A.E.S. died from. Tr. 164-65.

Dr. Shuman concluded that his opinions are plausible to his scientific mind but cannot be proven by laboratory experiment because no ethics program would allow the testing that would be needed on human infants. Tr. 166.

B. Petitioners' Expert, Dr. M. Eric Gershwin

1. Qualifications

Dr. Gershwin received his undergraduate degree from Syracuse University in 1966, and his medical degree from Stanford University in 1971. Pet. Ex. 64 at 1. He is board certified in allergy and clinical immunology, as well as internal medicine with a subspeciality in rheumatology. *Id*. at 2. Dr. Gershwin is currently the Director of the Allergy-Clinical Immunology Program and a Professor of Medicine (Rheumatology and Allergy) at the University of California Davis School of Medicine. *Id*. at 1-2.

2. Opinion

a. Dr. Gershwin's First Report

Dr. Gershwin acknowledged Drs. Shuman and Harris's agreement that the autopsy showed the brain weight to be heavier than normal and consistent with cerebral edema, which is unusual and not characteristic of SIDS. Pet. Ex. 63 at 1.

Dr. Gershwin submitted that A.E.S. received multiple vaccines which caused the cytokine production that is a plausible and likely explanation for the cerebral edema and enlarged brain found on autopsy that that led to death. Pet. Ex. 63 at 1-2. Dr. Gershwin explained that cytokine signaling at the BBB is a crucial feature of dynamic regulation, but the interface of cytokines with the BBB can also affect the function of the brain and cause disease. *Id*. While the BBB can selectively transport several cytokines including IL-1α, IL-1β, IL-1 receptor antagonist, IL-6, TNF-α, leukemia inhibitory factor, ciliary neurotrophic factor, and many adipokines, it can also restrict some cytokines from crossing the BBB with many cytokines and peptides being degraded

before reaching the central nervous system ("CNS") parenchyma. However, a lack of permeation does not prevent cytokines from affecting cerebral vascular functions, including modification of tight junction structures and endothelial signaling. *Id*. at 2.

According to Dr. Gershwin, cerebral edema is the clinical manifestation of inflammation. He referred to Dr. Shuman's opinion that A.E.S.'s cerebral edema resulted in axial herniation leading to her fatal outcome. Pet. Ex. 63 at 1.

b. Dr. Gershwin's Supplemental Report

Dr. Gershwin agreed there was no evidence of an excessive cytokine response following A.E.S.'s vaccination but submitted that no two individuals respond the same to vaccinations. Pet. Ex. 97 at 1. Two children can produce a similar level of cytokines from the same vaccination, but one may develop fever while the other may not. *Id.* Since an MRI or CT was not done, there is no information about the fine structure of A.E.S.'s brain. It is also unknown whether A.E.S. was genetically predisposed to brain edema, because genetic studies and sophisticated mapping of the brain for underlying target differences to be compared with other children would be required to confirm this. Importantly, however, the cerebral brain edema seen on autopsy was abnormal and cannot be explained other than by an underlying abnormality of her target tissue, which would make her more susceptible to cytokine-mediated inflammation. Simply stated, A.E.S. was more fragile. *Id*. Dr. Gershwin opined that the vaccinations were the "only logical explanation" for the neuropathology A.E.S. suffered. *Id*. at 2.

c. Dr. Gershwin's Testimony

At hearing, Dr. Gershwin conceded that the cytokines produced by the vaccinations received by A.E.S. was no more than expected. However, the objective finding of brain swelling was rare, therefore, "there had to be something that was defective on a genetic basis with a receptor in [A.E.S.'s] brain that essentially made her a susceptible host…" Tr. 181. Routine two-month-old vaccinations do not cause an acute encephalopathy, but if the host is susceptible with a "potpourri of cytokines, as you would expect to be produced by an innate or first-responder immune system…it is plausible." Tr. 182.

Dr. Gershwin explained that the immune system is designed to protect us from the outside world. Tr. 182. When exposed to an infection or a vaccine, the innate immune system begins to operate, producing immune cells called cytokines or chemokines which can do almost anything, like produce or prevent inflammation or lead to or reduce swelling. Tr. 183-84. These cytokines mediate and enable communication between the innate and adaptive immune systems as well as between innate cells and other body tissues. Tr. 184. The cytokines signal cell behavior for the whole body. Swelling means some other vessel, interstitial cell, or component is leaking fluid due to the presence of cytokines. Tr. 184. Vaccines produce cytokines and chemokines at the vaccine site which drain into the lymph nodes, circulate around the body, and can cross the blood brain barrier producing biologic effects. Tr. 185-88.

Dr. Gershwin discussed *Kashiwagi* to illustrate the presence of various cytokines after vaccination. Tr. 191-92, 201; Pet. Ex. 65.[24] In addition to the cytokines produced from the vaccination process, a protein, or "complement" is also produced which contributes to inflammation, "all of whom have implications for swelling of the brain if you have a genetic defect, a flaw." Tr. 188-89. Dr. Gershwin referenced *Hervé* to explain what happens when a vaccine enters the body and to provide the "logical and plausible explanation" for what occurred in this case. Tr. 194-95; Pet. Ex. 104.[25] *Hervé* showed that within minutes of a vaccination, resident immune cells including mass cells, monocytes, and macrophages are activated and release soluble factors, pro-inflammatory cytokines, chemokines, effectors of the complement cascade, and vasodilators. Tr. 195; Pet. Ex. 104 at 4. *Pan* illustrated the biology and mechanism that is well-established by the cited literature. Tr. 201-03; Pet. Ex. 66.[26]

Dr. Gershwin agreed that none of the articles propose that the cytokines released in response to vaccinations cross the blood brain barrier and cause cerebral edema but stated that is because of the rarity of the event. He explained that other than VAERS reports, "[t]here is no experimental study or observational study or case theories that I can cite that will support that that evidence has already been produced. I can produce what the logic is, discuss it with relation to [A.E.S.], but that is as far as I can go." Tr. 204. He added no one is going study such rare events, but the basis for the vaccine court is the idea that rare events occur. Tr. 205.

Dr. Gershwin referred to encephalopathy as the brain being "sick" which results from anything that injures oxygen delivery to the brain including trauma, stroke, constriction of a blood vessel, swelling from insult, infections, or neurodegenerative and autoimmune disorders. Tr. 195. Cytokines are "incredible players" in encephalopathy. They are produced in the periphery in response to vaccination but are also produced in the brain itself by the microglial cells. Tr. 196.

According to Dr. Gershwin, the nature of the encephalopathy dictates what other materials played a role, such as complement and prostaglandins. Tr. 197. Thousands of cytokines with different functions based on their locations were produced after the many vaccines A.E.S. received. Tr. 205. The proinflammatory cytokine variants of IL-1 and IL-6, for example, could be released causing cerebral edema, but no study was done following the vaccinations received by A.E.S. so he is unable to specify which cytokines were produced in her blood that crossed the blood brain barrier. Tr. 206. However, studies that have been done on infections such as influenza and Reyes Syndrome show that proinflammatory cytokines can cause encephalopathy. In his opinion proinflammatory cytokines can produce swelling and edema anywhere in the body, and there is "no reason to think that the brain is an exception." Tr. 206-07.

Dr. Gershwin disagreed that cytokines released after vaccinations are only a "drop in the bucket." The purpose of vaccination is to "fool the body" into thinking it has the infection. Tr. 315. He agreed that babies are faced with challenges all the time but that is different than the physiological events of mounting an immune response as described by *Hervé*. Tr. 315; Pet. Ex.

[24] Kashiwagi et al., *supra* note 21.
[25] Caroline Hervé et al., *The how's and what's of vaccine reactogenicity*, 4 NPJ VACCINES 39 (2019), filed as "Pet. Ex. 104."
[26] Weihong Pan et al., *Cytokine Signaling Modulates Blood-Brain Barrier Function*, 17 CURRENT PHARMACEUTICAL DESIGNS 3729 (2011), filed as "Pet. Ex. 66."

104.[27] *Hervé* showed that every vaccine has the capacity to activate PPR (pattern, recognition, and receptors). This involves a variety of cells in a "promiscuous" response that stimulates downstream events and the critical biology mediated by cytokines. Tr. 316-18; Pet. Ex. 104 at 2.[28] Notably, *Hervé* was authored by vaccine manufacturer GlaxoSmithKline and published in Nature, which has "the highest impact factor of any medical journal." Tr. 318-19. Dr. Gershwin further disagreed that immune responses in identical twins are the same. Tr. 319. He agreed that cytokines have a half-life of 19 minutes but noted that the immune response is a continuous event and while a given cytokine may only last minutes, it does not mean each starts and stops being produced in that time. Tr. 316. *Kashiwagi* showed the elevation of prostaglandins to be the same following one or three bacterial vaccines but noted the level was still higher than that found in the normal population. Tr. 315-16; Pet. Ex. 65.[29]

Dr. Gershwin stated that even though there was only a small portion of brain pathology for examination here, it showed significant swelling. Tr. 318. He added that prolonged QT Syndrome would not explain the dominant finding of edema and size of A.E.S.'s brain on autopsy. Tr. 314. While there is a role for inflammatory mediators in prolonged QT Syndrome and at least a report of ventricular arrhythmia in those who receive the flu vaccine, he disagreed that prolonged QT Syndrome played any role in this case. If it did, the role of cytokines in that condition would also need to be discussed. Tr. 314.

Dr. Gershwin concluded that the vaccinations received by A.E.S. were a substantial factor in causing encephalopathy and death. Tr. 197. The autopsy did not show infection or metabolic disorder; swelling on the brain was the only significant feature seen. The multiple vaccines A.E.S. received released cytokines and chemokines that entered the blood, crossed the blood brain barrier, and either individually or in combination activated her genetically susceptible brain or microglial cells to produce cerebral edema. Tr. 198-99. The fact that A.E.S.'s encephalopathy and death occurred so rapidly implies a cytokine-mediated event which is an immunological response as illustrated in *Hervé*. Tr. 199. The number of cytokines produced had no bearing on his opinion: "[t]here has to be a genetic basis" for her response to the vaccinations, and genetic events occur even though the vast majority are harmless. Tr. 199, 207. The temporal relationship is consistent with vaccine causation. Tr. 200.

C. Respondent's Expert, Dr. McCusker

1. Qualifications

Dr. McCusker a pediatric immunologist and allergist. She is currently an associate professor of pediatrics and division director of pediatric allergy, immunology, and dermatology at Montreal Children's Hospital at the McGill University Health Centre. She is also a clinician scientist at McGill University Research Institute. Resp. Ex. B; Tr. 261. She received her medical degree from McMaster University Medical School in 1993. Dr. McCusker is board certified in pediatrics and completed post-doctoral research in immunology. Resp. Ex. B at 2.

[27] Hervé et al., *supra* note 25.
[28] *Id*.
[29] Kashiwagi et al., *supra* note 21.

2. Opinion

a. Dr. McCusker's First Report

Dr. McCusker disagreed that A.E.S. suffered a "rapid but silent onset of encephalopathy with asymptomatic catastrophic cerebral edema" resulting from the vaccines she received or that the vaccines caused cytokine and complement activation that led to apoptosis in her brain and cerebral edema. Resp. Ex. A at 5-6.

Dr. McCusker explained that when the body encounters a pathogen, the innate immune system signals the release of proinflammatory mediators, including cytokines, which function to communicate information to immune cells to help direct the nature and magnitude of the developing immune response. Resp. Ex. A at 6. The initial cascade of inflammation from the cells released to the site of infection or trauma is usually transient and tightly regulated. *Id.* The cytokines released by the innate immune system include TNF-α, IL-6, IL-1β and the interferon family of cytokines; most responses induce cytokine release without any systemic symptoms. *Id*. Vaccination induces cytokine release causing local effects like pain and redness or systemic effects like fever and malaise. The purpose of the immune response is to decrease replication of the invading organism and increase the basal metabolic rate to allow for activation of the adaptive immune system which generates immunological memory. The effects of cytokines are limited and resolve with elimination of acute infection or with the adaptive immune response effectively neutralizing the pathogen. *Id*. Cytokine response from vaccination is less than cytokine response from a natural infection and the "innate system is comparatively poorly activated." *Id*. Subsequent exposure to the same pathogen in the form of antibodies results in rapid clearance of the pathogen from the body with only limited activation of the innate, proinflammatory pathways. Dr. McCusker opined "[t]here were no signs of significant cytokine activity in this child." *Id*.

Dr. McCusker disagreed that Prevnar 13 vaccine has demonstrated any association with encephalopathy post-licensure; the only side effects identified in studies include fever, irritability, and decreased or increased sleepiness. Resp. Ex. A at 5. Dr. McCusker submitted that the total IgG antibodies generated were the expected level for an infant, whether generated in response to the vaccine or to naturally acquired antigens. The antibodies are distributed throughout the body, not restricted to the intravascular compartment. *Id*.

Dr. McCusker discussed the implication of Long QT syndrome and other channelopathies in SUID and noted their appearance in 20% of SUID patients. She suggested A.E.S.'s younger sibling having prolonged QT after birth raised the possibility that A.E.S. did too. However, no genetic studies were done. Resp. Ex. A at 3, 7.

Dr. McCusker added that studies show no evidence of a causal relationship between vaccination and SIDS, with studies "sufficiently powered" to account for rare events providing epidemiological evidence for a temporal association only. Resp. Ex. A at 7. Dr. McCusker concluded that the medical examiner ruled this a SUID case, there was no evidence of cytokine activation, the mechanisms proposed by petitioners are not consistent with or supported by current literature, and there is no evidence that the vaccinations received by A.E.S. caused her death. *Id*.

b. Dr. McCusker's Supplemental Report

In her supplemental report, Dr. McCusker addressed the opinions of Drs. Gershwin and Harris. Resp. Ex. E.

Dr. McCusker referred to "cytokine" as a general term for cell-to-cell communication proteins, with most cytokine events occurring locally without significant systemic signaling. An example of a systemic cytokine effect would be fever caused by cytokines like IL-1β, IL-6, and TNF-α. Resp. Ex. E at 2. Cytokines are the initial response released at the site of trauma or infection, are transient, tightly regulated, and shape the innate and adaptive responses. Resp. Ex. E at 2. Over 50 cytokines have been identified, each bind to specific receptors, and the effect of the binding is dependent on the recipient cell. *Id*.

Dr. McCusker agreed that vaccinations activate immune responses in part through cytokine upregulation:

> [o]ne study of cytokine levels following vaccination of healthy volunteers demonstrated increases in IL6 and IL1β levels in peripheral blood which peaked at approximately 3 hours post vaccination. By 32 hours, these levels had normalized. In this study of healthy volunteers IL1β levels started at 4.7pg/ml and increased to a maximum of 4.8 pg/ml at 8 hours post vaccination. IL6 levels were 2.1 pg/ml at baseline and were maximal at 5.8 pg/ml at 8 hours and finally IL1Ra was 188 pg/ml at baseline and increased to a maximum of 413 pg/ml at 5 hours post vaccination.

Resp. Ex. E at 3 (citing Resp. Ex. E, Tab 3).[30]

Dr. McCusker described *Kashiwagi* as showing that within 48 hours of vaccination, serum cytokine levels are very low, with only small amounts of IL-6 and TNFα detected. The development of fever was independent of the cytokine levels in the blood. Resp. Ex. E at 3; Resp. Ex. E, Tab 4.[31] The data suggests that cytokines are produced and released by the peripheral immune system with no evidence that the levels are sufficient to influence the development of brain edema as theorized by petitioners' expert. Resp. Ex. E at 3.

Dr. McCusker disagreed that A.E.S. died from cytokines passing through or interacting with the BBB and causing life-ending edema. Resp. Ex. E at 3. She referred to *Suntharlingam*, which assessed the safety of a T-cell immunomodulatory agent that when injected into adults resulted in a "cytokine storm" or rapid systemic inflammatory response syndrome (SIRS), to show that no one developed signs of encephalopathy or significant brain edema even when extreme levels of peripheral cytokines were released. The neurological symptoms observed included delirium from high fever, partial amnesia, localized numbness, difficulty concentrating, and headaches Resp. Ex. E at 3; Resp. Ex. E, Tab 5.[32]

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[30] Aroon D. Hingorani et al., *Acute Systemic Inflammation Impairs Endothelium-Dependent Dilatation in Humans*, 102 CIRCULATION 994 (2000), filed as "Resp. Ex. E, Tab 3."
[31] Kashiwagi et al., *supra* note 21.
[32] Ganesh Sutharalingam et al., *Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412*, 355 N.E. J. MED. 1018 (2006), filed as "Resp. Ex. E, Tab 5."

Dr. McCusker cited *Ron-Harel* to explain that the microglial cells present in the normal brain release cytokines themselves, including IL-6 to maintain homeostasis. Resp. Ex. E at 3-4; Resp. Ex. E, Tab 6.[33] *Moidunny* showed that the cytokines present in the brain are essential for neuroprotection and neuromodulation. Resp. Ex. E at 4; Resp. Ex. E, Tab 7.[34] When exposed to stressors such as brain injury and neurodegeneration, these microglial cells increase the release of IL-1 and IL-6 to maintain homeostasis. Resp. Ex. E at 2, 4.

Dr. McCusker agreed that an overexpression of cytokines in the CNS can be detrimental to the brain and lead to cognitive defects. Resp. Ex. E at 4. *Quan* listed several ways peripheral inflammatory events may signal the brain and result in different effects including: localized inflammation which activates the CNS through local nerve stimulation but has no clinically significant CNS response; a greater local inflammation that signals the CNS through nerve stimulation but results in sickness behavior and fever; systemic inflammation that activates both neural and BBB-dependent neural-immune afferents; and significant immune challenge resulting in activation via the peripheral nerves and the BBB. Resp. Ex. E at 4; Resp. Ex. E, Tab 11.[35] The first two reflect responses from vaccination. Local cytokine production at the vaccination site stimulates the release of cytokines that may result in sickness behaviors with no evidence that these low concentrations of peripheral cytokines can result in brain edema or SIDS. Resp. Ex. E at 5.

Dr. McCusker contends that none of the literature relied on by petitioners support a theory that peripheral cytokines released following vaccination can generate life-ending brain edema. Resp. Ex. E at 5-7. Further, the literature shows that even a cytokine storm does not disrupt the BBB causing death. Resp. Ex. E at 7.

Dr. McCusker added that A.E.S. showed no clinical signs of immune activation, acute cerebral edema or increased intracranial pressure in the 90 minutes prior to being found unresponsive. Resp. Ex. E at 7. However, literature shows that Long QT Syndrome and other channelopathies are implicated in up to 20% of sudden infant deaths and there was a family history of Long QT Syndrome. Therefore, Long QT Syndrome is a plausible explanation for A.E.S.'s clinical picture. There is no evidence that the December 16, 2013 vaccinations contributed to A.E.S.'s death. *Id*.

c. Dr. McCusker's Testimony

Dr. McCusker had no concerns with the multiple vaccinations that A.E.S. received, stating that studies show no change in adverse events when adding vaccines to the vaccine schedule for infants. Tr. 262-64. In fact, vaccine cocktails contain hundreds of different antigens, while newborns are exposed to hundreds of thousands of antigens every day. Vaccines are "a bit of a drop in the bucket" in comparison to the antigens the body sees every day. Tr. 264.

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[33] Noga Ron-Harel et al., *Brain homeostasis is maintained by "danger" signals stimulating a supportive immune response with the brain's borders*, 25 BRAIN, BEHAVIOR, & IMMUNITY 1036 (2011), filed as "Resp. Ex. E, Tab 6."

[34] Shamsudheen Moidunny et al., *Interleukin-6-type cytokines in neuroprotection and neuromodulation: oncostatin M, but not leukemia inhibitory factor requires neuronal adenosine A_1 receptor function*, 114 J. NEUROCHEMISTRY 1667 (2010), filed as "Resp. Ex. E, Tab 7."

[35] Ning Quan, *In-depth conversation: Spectrum and kinetics of neuroimmune afferent pathways*, 40 BRAIN, BEHAVIOR, & IMMUNITY 1 (2014), filed as "Resp. Ex. E, Tab 11."

Dr. McCusker discussed *Kashiwagi* as showing that one or multiple vaccines do not result in significant dose-dependent cytokine expression in a person and in fact, patients receiving a single monovalent vaccine had the highest expression of certain cytokines. Thus, cytokine responsiveness to a vaccination does not have a dose/response relationship in infants. Tr. 266-71; Resp. Ex. E, Tab 4[36] at Tables 1 and 2. When noted that Tables 1 and 2 of *Kashiwagi* did not include the vaccines A.E.S. received because they did not exist at the time of the study, Dr. McCusker responded, "regardless of the number of antigens that have been given to the child, the variation in the cytokines expressed – a total amount of cytokines expressed is not significantly different whether it's one, two or three." Tr. 271-73. Therefore, giving the Prevnar 13 vaccine at the same time as the Tdap, Hib, polio, and other vaccines does not increase cytokines any more than what was shown on the tables in *Kashwagi*. Tr. 273. She admitted that *Kashiwagi* was the only study done on cytokine levels following vaccination, so the cytokines levels are not a "hundred percent." Tr. 273. However, based on the way the immune system works, a combination of vaccines does not seem to significantly increase or change the adverse events and inflammation; the cytokine levels are similar in range whether you give one, two, or three vaccines. Tr. 273-74.

Dr. McCusker stated that increasing the number of antigens actually decreases the efficacy of each component to stimulate their own response. Tr. 274. Therefore, from an immunological perspective, the question is not if the system is being blasted with too much stimulus, because the stimulus comes from the fixed amount of antigen, but rather whether one can synthesize appropriate immune responses to many different antigens at a given time. Tr. 274-75.

Dr. McCusker discussed *Hervé,* noting it was a review article, so the primary data is not available. Tr. 267; Pet. Ex. 104.[37] *Hervé* discussed the balance between reactogenicity, minimization of adverse events, and the need for controlled trials to make proper judgments about whether a vaccine is causally implicated in something. Tr. 276-77; Pet. Ex. 104.[38] *Hervé* also noted the difficulties in determining whether symptoms are caused by a vaccine or illness, since both share the same signs and symptoms. Tr. 276-77; Pet. Ex. 104 at 2. *Hervé* was a twin study where one was vaccinated and the other was given a placebo, then three weeks later, the opposite was done. 88 percent reported low grade fever, 24 percent reported moderate fever, and 7 percent reported high fever in the placebo group. This showed that much of what is attributed to vaccinations is not vaccine related. Tr. 277-78.

Dr. McCusker explained further that the symptoms of fever, malaise, and headache described in *Hervé* were the result of cytokine signaling at the inflammation site that stimulates the vagus nerve, and moves to the pituitary, "not the presence of cytokines that are crossing the blood-brain barrier." Tr. 278; Pet. Ex. 104[39] at 4. The process is like dropping a pebble in a pond: the largest circle is where the pebble goes in then it gets smaller and smaller the further away from the pebble it gets.[40] *Kashiwagi* shows that the cytokines are inactivating as they circulate away from the injection site. Tr. 278-79. Further, the half-life of IL-1β in circulation is about 19 minutes,

[36] Kashiwagi et al., *supra* note 21.
[37] Hervé et al., *supra* note 25.
[38] *Id.*
[39] *Id.*
[40] Common knowledge dictates that it is the reverse—the circles get larger as they move away from where the pebble is dropped.

so its ability to cause significant toxic damage and local symptoms is mediated by cytokines. Tr. 279-80. It takes three hours for vaccines to be detected in muscles, meaning cytokine release requires that amount of time before it can be seen in the lymph nodes. Tr. 280. Therefore, the behavioral changes described by the mother on the way home from the doctor's office would not be cytokine-mediated behaviors because they occurred prior to the time it takes for cytokines to be detectible in the muscle. Tr. 281.

Dr. McCusker stated there are many kinds of cytokines, which are all mechanistically the same: they all bind to receptors, the receptors tell them what to do, and they do what they are told. Tr. 283-84. However, the way the cytokines are regulated or released is different. Proinflammatory cytokines are involved in inflammation in the periphery, not necessarily in the CNS. Their role is to open the blood vessels to permit movement of cells to the area of inflammation: "[s]o if you don't see evidence of inflammatory cells at the site, you would hypothesize, at least reasonably, that the inflammation or the edema that you are seeing is not inflammatory edema." Tr. 284-85.

Dr. McCusker continued that the BBB exists to regulate what happens in the CNS and while a few cytokines can diffuse across the BBB, the diffusion is controlled. Tr. 285-86. The cytokines that diffuse across the BBB do so through a receptor which transports it across the BBB or through peripheral signaling through the vagus nerve. Tr. 286. Cytokines can also signal through receptors on the membrane, which signal the brain that something is happening. It does not necessarily mean the cytokine enters the CNS, but the brain gets the message that it's present. Tr. 286-87.

Dr. McCusker disagreed that A.E.S. had a genetic anomaly in the brain making her unable to process cytokines properly. However, assuming she did, a baby's system is stimulated so much in the first two months of life, it would have been apparent earlier and "probably embryologically lethal" if the brain was not able to handle cytokines properly. Tr. 288-89.

Dr. McCusker described SIDS as a catch-all phrase, which excludes infants who have an obvious cause of death. Within that catch-all is a group of children who would qualify as sudden unexplained infant death, "meaning that they don't qualify as SIDS" but the distinction is not often used. Tr. 289-90.

Dr. McCusker maintained that the literature she submitted showed no increase in the rate of death following vaccination. She acknowledged that *Moro* looked at mortality data from VAERS, a referral-based and not rigorously checked data site, but still believed it captured some data about SIDS. Tr. 290-91; Resp Ex. A, Tab 15.[41] *Von Kries* picked up a signal but felt more investigation was necessary, and this led to *Vennemann*. Both found there may be an increased risk of sudden death in older children, but no increase for two-month-olds so the study is inapplicable to A.E.S. Tr. 295-97; Pet. Ex. 144[42]; Resp. Ex. A, Tab 17.[43] *Vennemann* and *Kuna*, both large studies using meta-analysis to examine several different populations, found no

[41] Pedro L. Moro et al., *Deaths Reported to the Vaccine Adverse Event Reporting System, United States, 1997-2013*, 61 CLINICAL INFECTIOUS DISEASES 980 (2015), filed as "Resp. Ex. A, Tab 15."
[42] von Kries et al., *supra* note 22.
[43] M.M.T. Vennemann et al., *Do immunisations reduce the risk for SIDS? A meta-analysis*, 25 VACCINE 4875 (2007), filed as "Resp. Ex. A, Tab 17."

association between sudden infant death and vaccination. Tr. 291; Resp. Ex. A, Tab 17[44]; Resp. Ex. A, Tab 18.[45]

Dr. McCusker discussed *Traversa*, pointing out that it was a case series of low-level scientific rigor, significant methodological flaws, and findings more likely by chance than by causation. Tr. 292-95; Resp. Ex. A, Tab 16.[46] She acknowledged that all studies have some limitations, but the more patients and data involved, the better the possibility of finding "that low signal, that rare kid." None of the studies cited showed an association between infant death and vaccination. Tr. 295.

According to Dr. McCusker, A.E.S. had no clinical signs or symptoms of excessive cytokine activation or acute cerebral edema. Tr. 297. The father's description was not of an encephalopathic baby that would "send a parent running" to the ER. He described a sleepy baby similar to his other children after vaccinations. Tr. 298. The mother described A.E.S. as quiet on the ride home but not encephalopathic, adding that there could be many reasons for why A.E.S. was sleepy like a lot of activity that day, a change in routine, something going on before her receipt of vaccines, or normal behavior that the parents are remembering more acutely with hindsight. Tr. 298-99, 306.

Dr. McCusker stated in her years of practice seeing encephalopathic children in the ER, they are not quiet. They are in pain, won't and can't eat, are nauseous, and have severe headache and vomiting. If there was significant cerebral edema leading to increased cranial pressure, then significant changes to behavior would have been expected, "not soft behavioral changes as described." Tr. 299. The children she has treated had encephalitis due to viral infection, tumor, or metabolic issues, not vaccinations. She has seen two patients with axial herniation. Tr. 307.

On cross examination, Dr. McCusker stated that there is no explanation for why some children develop fever after vaccination and others do not, but all have genetic differences. Tr. 307-08. She disagreed that proinflammatory cytokines are released immediately following vaccination, stating that Dr. Gershwin's cited literature shows a three-hour timeframe exists for the release of proinflammatory mediators. There is an immediate, local release of proinflammatory cytokines at the injection site from the abrasion to the skin, not the content of the vaccine. Tr. 308-09. Dr. McCusker disagreed that cytokines can permeate the BBB in a dysregulated manner. Tr. 309.

Dr. McCusker described Long QT Syndrome as a cardiac arrythmia, meaning the heart becomes dysrhythmic and stops beating normally which is often genetic. Not all genetic causes are known, but the whole population is referred to as channelopathies: problems regulating the movement of fluids, solutes, sodium, potassium, magnesium, and calcium et cetera in and out of the cell. Channelopathies can lead to noninflammatory edema. Tr. 300-01. The literature shows that Long QT Syndrome is associated with 20% of sudden infant deaths. There is no literature that associates vaccines with sudden infant death. Tr. 303. A.E.S.'s younger sibling had Long QT

[44] *Id.*
[45] Ronny Kuhnert et al., *Reanalyses of case-control studies examining the temporal association between sudden infant death syndrome and vaccination*, 30 VACCINE 2349, filed as "Resp. Ex. A, Tab 18."
[46] Traversa et al., *supra* note 23.

Syndrome which could explain what happened to A.E.S. Tr. 301, 303. Dr. McCusker conceded she did not see A.E.S.'s siblings medical records and no genetic testing was done but offered Long QT Syndrome as "an important possibility to consider in the differential diagnosis", not a probability. Tr. 310-11.

In responding to whether the acellular pertussis vaccine can cause encephalopathy, Dr. McCusker stated it would depend on one's definition of encephalopathy. If it included a change of behavior, then yes. If defined as cerebral edema leading to mortality, "that has not been demonstrated in large studies." Tr. 312. She agreed the CDC cautions that encephalopathy following acellular pertussis vaccine is a contraindication to additional DTaP vaccines. Tr. 312.

d. Dr. McCusker's Post-Hearing Supplemental Report

Following the hearing, Dr. McCusker submitted additional literature and a supplemental report briefly summarizing the "small selection of available studies of safety and efficacy of combination vaccines and the rationale behind their use." Resp. Ex. F; Resp. Ex. F, Tabs 1-6.

D. Respondent's Expert, Dr. Brent Harris

1. Qualifications

Dr. Harris is a board certified anatomic and neuropathologist and neuropathologist, a member of the American Association of Neuropathologists, and a fellow of the College of American Pathologists. Resp. Ex. C at 1; Resp Ex. D at 1. He has practiced for 17 years at Stanford University Medical Center, Dartmouth Medical School, and Georgetown University Medical Center. He is currently an attending pathologist, tenured associate professor of neurology and pathology, and the director of neuropathology at Georgetown University Medical Center in Washington, DC. He is also the sole neuropathology consultant for the Washington, DC Office of the Chief Medical Examiner and Howard University Hospital, and serves as a neuropathology consultant for the Washington, DC Veterans' Administration Hospital. In each of these institutions, he has multiple roles as a clinical pathologist, educator, and physician-scientist researcher. Dr. Harris has reviewed over 10,000 surgical pathology and autopsy cases throughout his career, approximately 10% of which were pediatric cases. Resp. Ex. C at 1; Resp Ex. D at 1.

2. Opinion

a. Dr. Harris's Report

Dr. Harris noted that A.E.S. was a well baby on December 16, 2013. There were no signs typical of anaphylaxis after receipt of her vaccinations. Resp. Ex. C at 3-4.

Dr. Harris discussed the autopsy as showing no signs of trauma, malformation, or skin rashes with fixed, purple "liver (sic) mortis"[47] extending over the posterior surfaces of the body, except for pressure areas. Resp. Ex. C at 3. There were no pathological abnormalities of the brain,

[47] Livor mortis is the "discoloration appearing on dependent parts of the body after death, as a result of cessation of circulation, stagnation of blood, and settling of the body by gravity." *Livor mortis*, DORLAND'S 1055.

but the brain weighed 595g, not the expected 461-555g. The heart, lungs, and thymus were normal but for petechiae. The liver was congested. The gastrointestinal and genitourinary tracts were normal. There were no abnormalities reported in other organs or tissues. X-rays were normal. Histological findings included congestion in the liver, kidneys, lungs (with intra-alveolar edema), pancreas, spleen, and thymus (with focal intraparenchymal blood). The brain and adrenals were normal. Toxicology studies were negative. Metabolic screening and genetic studies and cultures were not performed. There was nothing untoward at the scene; the baby was found on her back without obstruction of the face. Resp. Ex. C at 3.

Dr. Harris believed the autopsy findings were "likely correct" and included that "the brain appears grossly swollen bilaterally on superior surfaces. Inferior and lateral surface photos of the brain are not provided. No gross description of laryngeal/tracheal edema/erythema is made." Resp. Ex. C at 4. Microscopic sections showed mild congestion in the lungs with some alveolar macrophages and proteinaceous material, several areas of bacterial collections in alveoli with no infection suspected, and some areas of acute hemorrhage in the thymus but no other significant pathological abnormalities seen from sections of the adrenals, liver, pancreas, kidney, spleen, lungs, colon, or heart. There were no excess eosinophils[48] noted in the organs. *Id*.

According to Dr. Harris, the autopsy was insufficient for a SIDS workup. Resp. Ex. C at 4. There were only small pieces of the brain sectioned and the hippocampus was not sampled bilaterally, which is important to rule out structural abnormalities that could produce seizures. The samples taken showed no ischemic or structural changes in the pyramidal and dentate areas. The medulla, a "key area" sometimes found to have abnormalities in SIDS cases, was not sampled. *Id*.

Dr. Harris acknowledged that there was "mild edema and congestion" in all fragments of brain tissue that was sampled, characterized by neuropil vacuolation and perivascular/perineuronal clearing, but submitted the findings were difficult to gage because fixation/processing of the tissue can also mimic edematous appearance. There were "[n]o significant reactive micro- or astrogliosis findings seen in the brain sections. Sections from other organs also show some degree of congestion but no findings of infection or metabolic abnormalities." Resp. Ex. C at 4.

Dr. Harris noted the cause of death was "undetermined" based on a history of no prior illness, no foul play, and no pathological findings to explain her death. Resp. Ex. C at 4. However, he added that a neuropathologist was not consulted and despite microscopic examination of the brain, the examination was minimal and incomplete. *Id*.

Dr. Harris discussed anaphylaxis as a rare reaction to vaccines, well-described in the literature for adults and children, but not described on autopsy in infants. Resp. Ex. C at 5. He added that there are no consistent pathological findings for anaphylaxis, but some include upper airway edema, airway mucus accumulation, hyperinflation of the lungs, pulmonary congestion and edema, eosinophils in many organs, and cutaneous erythema or edema. *Id*.; Resp. Ex. C, Tab 2.[49] He agreed there was pulmonary edema and congestion observed here but that is a common and

[48] An eosinophil is "a granular leukocyte with a nucleus that usually has two lobes connected by a slender thread of chromatin, and cytoplasm containing coarse, round granules that are uniform in size." *Eosinophils*, DORLAND'S 622.
[49] Paul A. Greenberger et al., *Fatal anaphylaxis: postmortem findings and associated comorbid diseases*, 98 ANN. ALLERGY ASTHMA IMMUNOLOGY 252 (2007), filed as "Resp. Ex. C, Tab 2."

non-specific finding in all age groups on autopsy. Excess eosinophils were not noted. Brain edema is not described in forensic anaphylaxis literature. Resp. Ex. C at 5.

Dr. Harris agreed SIDS cannot be invoked in this case because of an incomplete sampling of brain tissue, no clear environmental trigger, and the medical examiner did not conclude that SIDS was the cause of death. Resp. Ex. C at 5. Further, he agreed there was edema of the brain, though he referred to it as "mild". Finally, he agreed with the pathological descriptions of the lungs, heart, liver, and adrenals, but did not see possible early ischemic cell changes in the cortex of the brain or reactive gliosis. *Id*.

Dr. Harris agreed A.E.S. had a heavy brain with gross evidence of swelling and mild edema on microscopic examination but asserted that herniation is very difficult to assess on an infant brain at autopsy. Resp. Ex. C at 6. There was an insufficient finding of hypoxia-ischemia or infection to explain the edema. *Id*. He disagreed that *Dolgopol* applied in this case because it discussed the neuropathological changes in infants who died from pertussis infection encephalopathy with autopsies showing variable edema, hemorrhages, and neurodegeneration. While A.E.S. had mild edema, there were no hemorrhages or neurodegenerative changes seen and no signs of cell death on the brain tissue. *Id*.; Pet. Ex. 19.[50]

In Dr. Harris's opinion, the cause of death here is "unknown" because the autopsy was incomplete with inadequate brain tissue sampling to investigate for SIDS and no finding or history of suffocation. Resp. Ex. C at 6.

b. Dr. Harris's Testimony

At hearing, Dr. Harris discussed his research involving the study of how brain cells change from young to middle to old age and their relationship to normal biology or predisposition to neurodegenerative disease. Tr. 218-19. As a clinical and forensic neuropathologist, Dr. Harris consults with the DC Chief Medical Examiner, looks at autopsies, and examines the brain to determine the pathology for the cause of death. He is also the director of the brain bank at Georgetown, where tissue is retained with the permission of the family to study how different diseases occur. Tr. 219-21.

Dr. Harris has been a consultant to the medical examiner on SIDS cases for the past eight years and has seen 30-40 SIDS cases per year. Tr. 222. For infants under the age of one, a diagnosis of sudden infant death is broken into categories of unexplained or unexpected, and then subcategorized into SIDS, unexplained, or relating to suffocation. Tr. 221. When examining the brains of children in these cases, they look for genetic defects, metabolic diseases, structural changes of the hippocampi that can lead to seizures, infectious processes or organisms that can infect the brain, evidence of inflammation, and hypoxic ischemic changes. Tr. 224.

While deferring to the immunologist, Dr. Harris stated that anaphylaxis usually occurs within minutes of exposure causing skin changes, difficulty breathing, and excess eosinophils in the tissues. There was no testimony or clinical signs here of anaphylaxis. Tr. 227. With a

[50] Vera B. Dolgopol, *Changes in the Brain in Pertussis with Convulsions*, 46 ARCHIVES CLINICAL NEUROPSYCHOLOGY 477 (1941), filed as "Pet. Ex. 19."

hypersensitivity reaction, he would expect to see redness and swelling at the injection site and enlargement of the lungs with pulmonary edema. By six hours later, there would be increased numbers of eosinophils in multiple tissues including the lungs and airways and at the local site where the drug was delivered. He would not expect to see cerebral edema. Tr. 229-30.

Dr. Harris stated that the final diagnoses contained in the autopsy report represent the "bottom line big picture" of the medical examiner's most important findings. Here, the final autopsy findings included thymic, epicardial, and pleural petechiae, pulmonary edema, and visceral congestion. However, pulmonary edema is a nonspecific though significant finding that could be seen in conditions other than hypersensitivity reaction. Tr. 245-47, 252. Cerebral edema was not included under autopsy findings. Tr. 256-57.

Dr. Harris explained that tissue viewed during autopsy is not fresh; it goes through a fixation process to help allow for better staining and stability under a microscope. Sometimes, the fixation process changes the tissue, and it becomes vacuolated.[51] Tr. 230. Therefore, when examining the tissue, one must recognize that vacuolation of the brain tissue is an artifact, "meaning it doesn't have anything to do with a patient's condition." Tr. 230. However, based on the brain heaviness here, photographs that suggested swelling of the brain, and microscopic observations, he was "fairly comfortable to say that this is more likely edema rather than an artifact of fixation." Tr. 231.

Dr. Harris stated that A.E.S.'s brain was significantly heavier than expected for a child her age. The swelling or edema of the brain was "an abnormal finding or a pathological finding. It's not normal. But we don't know what the cause of that swelling is in many cases of infant death, sadly." Tr. 231-32. The brain weight was a "pathological abnormality" with no infection. Tr. 250-51. The congestion in the organs was also a pathological abnormality. Tr. 251.

Noting that he is a pathologist and not an immunologist, neurologist, or pediatrician, he described "encephalopathy" as a nonspecific, clinical term for dysfunction of the brain. He noted that a pathology report would never contain a diagnosis of encephalopathy. Tr. 231-32.

Dr. Harris described the many types of different cells that make up the brain, particularly glial cells, which have different subtypes and functions. Tr. 235. Glial cells serve as markers for problems happening in the brain, including trauma, hypoxia, ischemia, brain tumors, and reactions to inflammatory cells. Their shape and appearance under the microscope change when they become reactive. Tr. 235-36. Hypoxia (low oxygen) and/or ischemia (low blood flow) cause a "cascade of changes" to the brain tissue which can be seen microscopically. Tr. 233-34. Seeing these changes in infant brain tissue is more challenging, but the earliest change would be seen as edema 6-12 hours after a hypoxic and/or ischemic event. 12-18 hours later, neurons would appear shrunken and redder in color. Tr. 234. Dr. Harris claimed that while he did not see signs of hypoxia or ischemia on the autopsy slides, he could not dispute that the edema that was seen was early signs of a hypoxia or ischemic event. He would want to see more areas of brain tissue samples to make that judgment. He could only say that usually it requires at least six hours for these changes to be seen. Tr. 235.

[51] Vacuoles are any membrane-bound space or cavity within a cell. *Vacuole*, DORLAND'S 1988. Vacuolated means containing vacuoles. *Vacuolated*, DORLAND'S 1987.

Initially, Dr. Harris stated that he did not see evidence of herniation on the superior surface of the brain. Tr. 236. He concurred that the gelatinous nature of the brain tissue makes it more challenging to observe herniation and that other signs, such as internal and external hemorrhage with downward herniation of the brainstem, may be present with herniation but were not mentioned by the medical examiner. An experienced neuropathologist would recognize early herniation even in infant cases, but he could not speak to the medical examiner's level of competence. Tr. 237-38. He noted that key sections of the brain were not sampled including the brainstem, which is the most detrimental area of herniation; "…not having those makes it very difficult, unfortunately, to say whether or not there was herniation in this case." Tr. 236-37. However, he could not "rule it out or rule in it" from a pathological standpoint. Tr. 237, 256.

When further pressed on whether brainstem herniation occurred in this case, Dr. Harris repeated the challenges of making a judgment without imaging studies or a full examination of the brain, adding that even with the degree of swelling on the surface of the brain, overall weight of the brain, and what he heard clinically, he could not rule it in or rule it out. Tr. 238-39. He could only say that the pathological evidence showed mild cerebral edema, and the medical examiner was appropriate in concluding the cause of death was undetermined; he probably would have done the same. Tr. 240.

Dr. Harris then discussed the literature on SIDS stating it does not often discuss vaccinations, and when it does "it's all over the place." Temporal proximity of SIDS to vaccination does not suggest a relationship, especially since SIDS usually occurs between one month and one year of age, the same timeframe during which vaccines are given. There is no clear causation or temporal relationship found between SIDS and an immunization or other medication. Tr. 241.

However, Dr. Harris stated this is not a SIDS case because "[b]y definition you cannot make a diagnosis of SIDS without a full sampling of the tissues." Tr. 243, 252. The sampling of the lungs and brain taken were insufficient, with no samples of the brainstem done, which is a necessary step to determining SIDS. Tr. 225, 252-53. His review of the autopsy slides showed a fair amount of congestion or increased blood within the vessels in all the organs but no inflammation suggestive of infectious disease or eosinophils indicative of a hypersensitivity reaction or anaphylaxis. Tr. 226. There was "only a very, very small sampling of brain tissue", but there was edema around the cells without malformation seen. Tr. 226. There were no clear environmental factors for a diagnosis of SIDS found, either. Tr. 253-54; Resp. Ex. C at 5. Based on the evidence, SIDS cannot be invoked in this case, and Dr. Harris agreed with the medical examiner that there was no conclusive cause of death. Tr. 254.

Dr. Harris stated the testimony about A.E.S.'s hyperextension of her neck when found gave him pause for possible suffocation though he had never seen hyperextension of the neck cause an airway problem. Tr. 244, 254. He agreed that the term "hyperreflexia" was contained on the investigation report which he reviewed but had not given much thought to until he heard the testimony. He was then asked by respondent's counsel if he could still exclude SIDS in this case. Tr. 257. Petitioners' counsel objected, stating that Dr. Harris had all the information in his possession when he issued his opinions in this case, including his opinion that this was not a SIDS case, and to opine differently now would amount to a new opinion. Tr. 258. I agreed that if Dr. Harris was to now say he could not rule out SIDS in this case, he would be contradicting his own

testimony. Also, Mr. Kennedy had testified that "hyperextension" was the only option on his form and was not a word used by the father. Further, I would be unable to accept a suggestion that a baby of this age who moves and turns their head upward while on their back could suffocate themselves. Therefore, Mr. Kennedy's testimony explaining why he checked "hyperextension" on the form, Mr. Sims's description of how he found A.E.S., and Dr. Harris's testimony based on the evidence, points to an unexplained death rather than a SIDS case. Tr. 258-59. Respondent's counsel stated that he was not asking Dr. Harris to change his answer. I advised that all the evidence would be weighed when the time came for a decision in this case. Tr. 259.

Dr. Harris concluded that he did not believe vaccines were the cause of A.E.S.'s death. Tr. 241-42. When asked, based on the evidence, if he could definitively say that her death was not the result of her vaccines, he stated "[y]eah, I base my opinion, though, on the medical literature and the fact that the timing of this autopsy or of the vaccination could not have been an anaphylactic reaction. And I'm not aware of any literature to suggest that vaccination other than anaphylaxis could lead to a death like this." Tr. 242. However, "[he didn't] have an explanation for another diagnosis in this case." Tr. 242-43. There was no trauma and no evidence of neurological disease other than edema. Tr. 255-56.

VII. Applicable Law

A. Legal Standard Regarding Causation

The Vaccine Act provides two avenues for petitioners to receive compensation. First, a petitioners may demonstrate a "Table" injury—i.e., an injury listed on the Vaccine Injury Table that occurred within the provided time period. § 11(c)(1)(C)(i). "In such a case, causation is presumed." *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1320 (Fed. Cir. 2006); *see* § 13(a)(1)(B). Second, where the alleged injury is not listed on the Vaccine Injury Table, a petitioners may demonstrate an "off-Table" injury, which requires that the petitioners "prove by a preponderance of the evidence that the vaccine at issue caused the injury." *Capizzano*, 440 F.3d at 1320; *see* § 11(c)(1)(C)(ii). Initially, a petitioners must provide evidence that he or she suffered, or continues to suffer, from a definitive injury. *Broekelschen v. Sec'y of Health & Human Servs*., 618 F.3d 1339, 1346 (Fed. Cir. 2010). A petitioners need not show that the vaccination was the sole cause, or even the predominant cause, of the alleged injury; showing that the vaccination was a "substantial factor" and a "but for" cause of the injury is sufficient for recovery. *See Pafford v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1355 (Fed. Cir. 2006); *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999).[52]

To prove causation for an "off-Table" injury, petitioners must satisfy the three-pronged test established in *Althen v. Sec'y of Health & Human Servs*., 418 F.3d 1274 (Fed. Cir. 2005). *Althen* requires that petitioners show by preponderant evidence that a vaccination petitioners received caused his or her injury "by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the

[52] The Vaccine Act also requires petitioners to show by preponderant evidence the vaccinee suffered from the "residual effects or complications" of the alleged vaccine-related injury for more than six months, died from the alleged vaccine-related injury, or required inpatient hospitalization and surgical intervention as a result of the alleged vaccine-related injury. § 11(c)(1)(D). It is undisputed that this requirement is satisfied in this case.

reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id*. at 1278. Together, these prongs 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.'" *Stone v. Sec'y of Health & Human Servs*., 676 F.3d 1373, 1379 (Fed. Cir. 2012) (quoting *Shyface*, 165 F.3d at 1352-53). 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 Health & Human Servs*., 35 F.3d 543, 548 (Fed. Cir. 1994). Petitioners are not required to identify "specific biological mechanisms" to establish causation, nor are they required to present "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities." *Capizzano*, 440 F.3d at 1325 (quoting *Althen*, 418 F.3d at 1280). "[C]lose calls regarding causation are resolved in favor of injured claimants." *Althen*, 418 F.3d at 1280.

Each of the *Althen* prongs requires a different showing. The first *Althen* prong requires petitioners to provide a "reputable medical theory" demonstrating that the vaccines received *can* cause the type of injury alleged. *Pafford*, 451 F.3d at 1355-56 (citation omitted). To satisfy this prong, petitioners's "theory of causation must be supported by a 'reputable medical or scientific explanation.'" *Andreu ex rel. Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1379 (Fed. Cir. 2009) (quoting *Althen*, 418 F.3d at 1278). This theory need only be "legally probable, not medically or scientifically certain." *Id.* at 1380 (emphasis omitted) (quoting *Knudsen*, 35 F.3d at 548). Nevertheless, "petitioners [must] proffer trustworthy testimony from experts who can find support for their theories in medical literature." *LaLonde v. Sec'y of Health & Human Servs.*, 746 F.3d 1334, 1341 (Fed. Cir. 2014).

The second *Althen* prong requires proof of a "logical sequence of cause and effect." *Capizzano*, 440 F.3d at 1326 (quoting *Althen*, 418 F.3d at 1278). In other words, even if the vaccinations can cause the injury, petitioners must show "that it did so in [this] particular case." *Hodges v. Sec'y of Health & Human Servs.*, 9 F.3d 958, 962 n.4 (Fed. Cir. 1993) (citation omitted). "A reputable medical or scientific explanation must support this logical sequence of cause and effect," *id.* at 961 (citation omitted), and "treating physicians are likely to be in the best position to determine whether a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury," *Paluck v. Sec'y of Health & Human Servs.*, 786 F.3d 1373, 1385 (Fed. Cir. 2015) (quoting *Andreu*, 569 F.3d at 1375). Petitioners is not, however, required "to eliminate alternative causes as part of establishing [their] prima facie case." *Doe v. Sec'y of Health & Human Servs.*, 601 F.3d 1349, 1357-58 (Fed. Cir. 2010); *see Walther v. Sec'y of Health & Human Servs.*, 485 F.3d 1146, 1152 (Fed. Cir. 2007) (holding that a "petitioners does not bear the burden of eliminating alternative independent potential causes").

To satisfy the third *Althen* prong, petitioners must establish a "proximate temporal relationship" between the vaccination and the alleged injury. *Althen*, 418 F.3d at 1281. This "requires preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *De Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). Typically, "a petitioners's failure to satisfy the proximate temporal relationship prong is due to the fact that onset was too late after the administration of a vaccine for the vaccine to be the cause." *Id.* However, "cases in which onset is too soon" also fail this prong; "in either case, the temporal relationship is not such that it is medically acceptable to conclude that the vaccination

and the injury are causally linked." *Id.*; *see also Locane v. Sec'y of Health & Human Servs.*, 685 F.3d 1375, 1381 (Fed. Cir. 2012) ("[If] the illness was present before the vaccine was administered, logically, the vaccine could not have caused the illness.").

B. Legal Standard Regarding Fact Finding

The process for making factual determinations in Vaccine Program cases begins with analyzing the medical records, which are required to be filed with the petition. § 11(c)(2). Medical records created contemporaneously with the events they describe are presumed to be accurate and "complete" such that they present all relevant information on a patient's health problems. *Cucuras v. Sec'y of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993). In making contemporaneous reports, "accuracy has an extra premium" given that the "proper treatment hang[s] in the balance." *Id.* Contemporaneous medical records that are clear, consistent, and complete warrant substantial weight "as trustworthy evidence." *Id*. Indeed, "where later testimony conflicts with earlier contemporaneous documents, courts generally give the contemporaneous documentation more weight." *Campbell ex rel. Campbell v. Sec'y of Health & Human Servs.*, 69 Fed. Cl. 775, 779 (2006); *see United States v. U.S. Gypsum Co.*, 333 U.S. 364, 396 (1948). But petitioners can support their claim with oral testimony if it is credible and consistent with the medical records. *See, e.g.*, *Stevenson ex rel. Stevenson v. Sec'y of Health & Human Servs.*, No. 90-2127V, 1994 WL 808592, at *7 (Fed. Cl. Spec. Mstr. June 27, 1994) (crediting the testimony of a fact witness whose "memory was sound" and "recollections were consistent with the other factual evidence"). In short, "the record as a whole" must be considered. § 13(a).

C. Evaluating Expert Testimony

Establishing a sound and reliable medical theory connecting the vaccine to the injury often requires a petitioner to present expert testimony in support of his or her claim. *Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1361 (Fed. Cir. 2000). The Supreme Court's opinion in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), requires that courts determine the reliability of an expert opinion before it may be considered as evidence. "In short, the requirement that an expert's testimony pertain to 'scientific knowledge' establishes a standard of evidentiary reliability." *Id*. at 590 (citation omitted). Thus, for Vaccine Act claims, a "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." *Moberly ex rel. Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1324 (Fed. Cir. 2010). The *Daubert* factors are used in the *weighing* of the reliability of scientific evidence proffered. *Davis v. Sec'y of Health & Human Servs.*, 94 Fed. Cl. 53, 66-67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"). Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen*, 618 F.3d at 1347 (citing *Lampe*, 219 F.3d at 1362). And nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder ex rel. Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 743 (2009) (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)).

D. Consideration of Medical Literature

Finally, although this decision discusses some but not all the literature in detail, the undersigned reviewed and considered all of the medical records and literature submitted in this matter. *See Moriarty ex rel. Moriarty v. Sec'y of Health & Human Servs.*, 844 F.3d 1322, 1328 (Fed. Cir. 2016) ("We generally presume that a special master considered the relevant record evidence even though [s]he does not explicitly reference such evidence in h[er] decision."); *Simanski v. Sec'y of Health & Human Servs.*, 115 Fed. Cl. 407, 436 (2014) ("[A] Special Master is 'not required to discuss every piece of evidence or testimony in her decision.'" (citation omitted)), *aff'd*, 601 F. App'x 982 (Fed. Cir. 2015).

XI. Discussion

Petitioners allege that the vaccines administered to A.E.S. caused her to suffer a Table encephalopathy and death, or alternatively, resulted in an off-Table encephalopathy and death.

Drs. Shuman and Harris agree this case does not meet the criteria for SIDS. Pet. Ex. 16 at 24, 26-29; Resp. Ex. C at 4-6. "I agree [with Dr. Shuman] that SIDS cannot be invoked in this case, as an incomplete sampling of brain tissue and no clear environmental trigger is present. The medical examiner also did not diagnose the death as SIDS." Resp. Ex. C at 5; Tr. 243, 253-54.

Therefore, this case involves an 11-week-old infant who died between six and seven hours following the receipt of her first set of multiple vaccinations and had a finding of brain swelling/edema with pulmonary and cardiovascular congestion on autopsy. The cause of death was "undetermined." *See* Pet. Ex. 7 at 3.

A. A.E.S. suffered a Table encephalopathy and death.

The Qualifications and Aids to Interpretation (QAI) to the Vaccine Injury Table defines an encephalopathy occurring within 72 hours of a DTaP vaccine as a Table injury:

> (2) *Encephalopathy.* For purposes of paragraph (a) of this section, a vaccine recipient shall be considered to have suffered an encephalopathy only if such recipient manifests, within the applicable period, an injury meeting the description below of an acute encephalopathy, and then a chronic encephalopathy persists in such person for more than 6 months beyond the date of vaccination.
>
> (i) An acute encephalopathy is one that is sufficiently severe to require hospitalization (whether or not hospitalization occurred).
>
> (A) *For children less than 18 months of age* who present without an associated seizure event, an acute encephalopathy is indicated by a significantly decreased level of consciousness lasting for at least 24 hours. Those children less than 18 months of age who present following a seizure shall be viewed as having an acute encephalopathy if their

significantly decreased level of consciousness persists beyond 24 hours and cannot be attributed to a postictal state (seizure) or medication.

* * *

(C) Increased intracranial pressure may be a clinical feature of acute encephalopathy in any age group.

(D) A "significantly decreased level of consciousness" is indicated by the presence of at least one of the following clinical signs for at least 24 hours or greater (see paragraphs (b)(2)(i)(A) and (b)(2)(i)(B) of this section for applicable timeframes):

(1) Decreased or absent response to environment (responds, if at all, only to loud voice or painful stimuli);

(2) Decreased or absent eye contact (does not fix gaze upon family members or other individuals); or

(3) Inconsistent or absent responses to external stimuli (does not recognize familiar people or things).

(E) The following clinical features alone, or in combination, do not demonstrate an acute encephalopathy or a significant change in either mental status or level of consciousness as described above: Sleepiness, irritability (fussiness), high-pitched and unusual screaming, persistent inconsolable crying, and bulging fontanelle. Seizures in themselves are not sufficient to constitute a diagnosis of encephalopathy. In the absence of other evidence of an acute encephalopathy, seizures shall not be viewed as the first symptom or manifestation of the onset of an acute encephalopathy.

* * *

(iii) An encephalopathy shall not be considered to be a condition set forth in the Table if in a proceeding on a petition, it is shown by a preponderance of the evidence that the encephalopathy was caused by an infection, a toxin, a metabolic disturbance, a structural lesion, a genetic disorder or trauma (without regard to whether the cause of the infection, toxin, trauma, metabolic disturbance, structural lesion or genetic disorder is known). If at the time a decision is made on a petition filed under section 2111(b) of the Act for a vaccine-related injury or death, it is not possible to determine the cause by a preponderance of the evidence of an encephalopathy, the encephalopathy shall be considered to be a condition set forth in the Table.

(iv) In determining whether or not an encephalopathy is a condition set forth in the Table, the Court shall consider the entire medical record.

See 42 C.F.R. § 100.3(b)(2) (effective July 23, 2015 to March 20, 2017).

In their post-hearing filings, petitioners argued that:

> the Federal Circuit in *Jay v. Secretary of HHS,* 998 F.2d 979, 983 (Fed. Cir. 1993), held, "[w]e can find nothing in the Vaccine Act which precludes death from being used as evidence of a table injury, here encephalopathy." "[T]here is no more profound and permanent change in the level of consciousness than death." *Id*. at 983 n.6. "Thus, according to the Federal Circuit, the special master must consider the fact of death together with the other evidence in an on-Table encephalopathy case." *Kincaid v. Sec'y of HHS*, Case No. 02-1766V, 2003 U.S. Claims LEXIS 403, 2003 WL 23119834 *24 (Fed. Cl. Spec. Mstr. Nov. 26, 2003) (citing *Jay v. Secretary of HHS*, 998 F. 2d. 979, 983 (Fed. Cir. 1993). Also, the fact that a vaccinee has a table encephalopathy but dies before the number of hours required under the table does not defeat a petitioner's table claim. *See Kincaid v. Sec'y of HHS; Williams v. Sec'y of HHS; Sword v. Sec'y of HHS*.

See Petitioners' Post-Hearing Brief ("Pet. Post-H Brief") at 8.

Respondent argued that the cases petitioners relied on are over 20 years old. Respondent's Post-Hearing Brief ("Resp. Post-H Brief") at 9. The Court of Federal Claims has since addressed *Jay* in *Waterman v. Sec'y of Health & Human Servs.*, 123 Fed. Cl. 564, 575 (2015) (citing *Hodges v. HHS*, 9 F.3d 958, 960 (Fed. Cir. 1993) and quoting *Hellebrand v. Sec'y of Health & Human Servs.*, 999 F.2d. 1565, 1571 (Fed. Cir. 1993), noting that death does not independently establish the existence of a Table Injury, and to conclude so regarding any death that occurs within 72 hours of receipt of a DTaP vaccine would be at odds with the plain language of the Vaccine Act. Resp. Post-H Brief at 9. Thus, petitioners must rely on more than just A.E.S.'s death and must prove that an acute encephalopathy as defined in the QAI occurred prior to her death, with her death occurring as a sequela of the acute encephalopathy. *Id*.

The parties agreed that the applicable definition of acute encephalopathy is "a significantly decreased level of consciousness lasting for at least 24 hours." Respondent's Pre-Hearing Submission ("Resp. Pre-H Sub.") at 6 (citing 42 C.F.R. § 100.3(b)(2)(i)(A) (effective July 23, 2015 to March 20, 2017).

However, respondent argued that death does not independently establish the existence of a Table Injury; petitioners must rely on more than just death and must prove that an acute encephalopathy as defined in the QAI occurred prior to her death, with death occurring as a sequela of the acute encephalopathy; the QAI definition of acute encephalopathy is "a significantly decreased level of consciousness lasting for at least 24 hours"; and petitioner "cannot prove that A.E.S. suffered from a significantly decreased level of consciousness for at least 24 hours, because she died less than 24 hours after her vaccinations." Resp. Post-H Brief at 9; Resp. Pre-H Sub at 4.

Respondent's argument suggests the impossible in a situation where a death occurs in less than 24 hours. The clinical features of an encephalopathy clearly cannot exist for 24 hours when death occurs before that time. However, respondent's argument relies on only part of the statute. The regulation continues with exceptions to a finding of encephalopathy:

> an encephalopathy shall not be considered to be a condition set forth in the Table if in a proceeding on a petition, it is shown by a preponderance of the evidence that the encephalopathy was caused by an infection, a toxin, a metabolic disturbance, a structural lesion, a genetic disorder or trauma (without regard to whether the cause of the infection, toxin, trauma, metabolic disturbance, structural lesion or genetic disorder is known)

42 C.F.R. § 100.3(b)(2)(iii). All the above were ruled out in this case. Here, the experts agree and the medical records and autopsy report support that there was no infectious process, metabolic disorder, pathological anomalies, trauma, prenatal or perinatal CNS injury found, only swelling and inflammation of the brain on autopsy.

The regulation continues, "[i]f at the time a decision is made on a petition filed under section 2111(b) of the Act for a vaccine-related injury or death, it is not possible to determine the cause by a preponderance of the evidence of an encephalopathy, the encephalopathy shall be considered to be a condition set forth in the Table." Further, "[i]n determining whether or not an encephalopathy is a condition set forth in the Table, the Court shall consider the entire medical record." *See* 42 C.F.R. § 100.3(b)(2)(iii-iv) (effective July 23, 2015 to March 20, 2017).

Here, a preponderance of the evidence shows that A.E.S. was a well 11-week-old baby when she received her vaccinations between 11:00 and 11:30 am on December 16, 2013. Pet. Ex. 2 at 16-20; Pet. Ex. 7 at 9. While there are some discrepancies in the record, Mr. Sims recalled giving A.E.S. a bottle before putting her in her bassinet at approximately 5:30 pm. He noted that she ate more slowly than usual and seemed uninterested. Tr. 55-56, 77; Pet. Ex. 136 at 2. However, Mrs. Sims stated that A.E.S. appeared to breastfeed more for comfort because she was not feeling well throughout the afternoon before Mrs. Sims went to work, but she was uncertain if A.E.S. was actually eating. Tr. 21-22. The autopsy did not mention any food content in the stomach. Pet. Ex. 7 at 4-5. Further, the parents described A.E.S. that afternoon as sleeping more, only opening her eyes sometime but not making eye contact, not tracking, having a distant look as though looking past her mother, not cuddling, fussing and whining as if she had a headache. Tr. 21-22, 40, 59-60; Pet. Ex. 135 at 2. At approximately 5:30 pm, six and a half hours after her vaccinations, she was placed on her back in her bassinet. At around 6:15 pm, she was found face up on her back with her head tilted upward to the left, hand clenched, pale, and blue around her lips. Pet. Ex. 7 at 7-9; Tr. 57-58. Dr. Shuman referred to her positioning as a decerebrate posture, a sign of axial herniation and encephalopathy. Tr. 140. When she was picked up, A.E.S. was limp but warm to the touch, and Mr. Sims thought he felt her move and exhale. Tr. 62-63; Pet. Ex. 136 at 2; Pet. Ex. 7 at 7-9. She was unresponsive upon arrival at the hospital. Pet. Ex. 5 at 10-12. Cardiac rhythm strips showed evidence of some electro-cardiac activity, but she had no pulse and resuscitation efforts were unsuccessful. *Id*. at 12, 55-56, 58. She was pronounced dead at 7:15 p.m., approximately eight hours after her vaccinations. *Id*. at 10-12, 57-58. The autopsy revealed a heavy brain at 595g compared to an expected 461-555g, and cerebral edema. Pet. Ex. 3 at 3. The cause and manner of death was listed as undetermined and "consistent with Sudden Unexplained Infant Death (SUID)." *Id*. at 4.

Drs. Shuman and Harris agreed the brain was heavy and there was cerebral edema. *See* Pet. Ex. 16 at 31; Pet. Ex. 92 at 1-2; Resp. Ex. C at 3-4, 6; Tr. 133-140, 231-32; 250-52. Dr. Gershwin referred to cerebral edema as the clinical manifestation of inflammation. Pet. Ex. 63 at 1.

It is undisputed that there is no evidence that A.E.S. died of a factor unrelated to the administration of the vaccines. In fact, Dr. Harris admitted he didn't "have an explanation for another diagnosis in this case." Tr. 242-43. Dr. McCusker suggested the possibility of a condition suffered briefly by a sibling born after A.E.S.'s death, but she could not say that it was probable that A.E.S. had that condition. She conceded she never reviewed the sibling's records nor was any genetic testing done. Tr. 310-11.

Further, the regulation provides that "[i]ncreased intracranial pressure may be a clinical feature of acute encephalopathy in any age group." 42 C.F.R. § 100.3(b)(2)(i)(C) (effective July 23, 2015 to March 20, 2017). Both Drs. Shuman and Harris agreed that A.E.S.'s brain was abnormally heavy with edema on autopsy. Dr. Shuman concluded that A.E.S. developed an encephalopathy with cerebral edema which caused axial herniation that led to her death. Pet. Ex. 16 at 36-37; *see* Pet. Ex. 92. Dr. Harris agreed that the brain was abnormally heavy and that there was edema, but did not see early ischemic injury, reactive gliosis, hemorrhage, or neurodegenerative changes, or evidence of cell death. Resp. Ex. C at 5-6. However, he could not refute that the edema seen on autopsy was not an early sign of hypoxia-ischemia although it usually takes 6-12 hours for such changes to be seen as edema. Tr. 233-34. Further, Dr. Harris could not rule out axial herniation as described by Dr. Shuman. Tr. 236-37, 256. Both experts agreed that once the skull was removed on autopsy, the brain would move back into place, relieving the pressure caused by swelling within the closed compartment of the brain. Pet. Ex. 16 at 31; Tr. 236-37. Thus, the existence of intracranial pressure cannot be ruled out.

Further, while respondent's experts argued that A.E.S. did not show behaviors of an encephalopathic child, they agreed that a systemic reaction severe enough to cause characteristic and perceptible encephalopathic behaviors would have required at least six to eight hours, which is the exact time frame from the time A.E.S. received her vaccines until she was found unresponsive in her bassinet. *See* Tr. 235; Pet. Ex. 7 at 7, 9. It is unknown what transpired while A.E.S. was in her bassinet alone between approximately 5:30 and 6:15 pm. Respondent argues that A.E.S. did not suffer a systemic reaction because there was no contemporaneous observation of a reaction, but reaching such a conclusion would be unreasonable. The absence of any report of a systemic reaction such as high fever or seizure is of limited value and merely shows that no reaction was recorded, not that a reaction did not occur when A.E.S. was unobserved during her last 45 minutes of responsive life. A.E.S.'s positioning when she was found by her father—pale with blue lips, fists clenched, and head upward to the left—suggests that something occurred, even if it was not witnessed. The result was the death of an 11-week-old child with no cause of death found on autopsy and a heavy brain and cerebral edema agreed to be pathologically abnormal.

We do not have the luxury of knowing what A.E.S.'s behaviors would have been had she survived. We have only the reports of the parents about her behavior in the afternoon following receipt of her vaccines that morning: she was sleepy and fussy, not making eye contact, not cuddling, feeding slowly, appearing "out of it", not looking at her mother and not tracking. Dr. Shuman opined that these behaviors are demonstrative of A.E.S. being encephalopathic based on the behavioral repertoire of an 11-week-old. Tr. 140-41. The autopsy showed a brain heavier than normal for a baby her age. *See* Pet. Ex. 7 at 5. Although the autopsy was arguably deficient, there is no dispute among the pathologists that tissue samples taken showed swelling of the brain. *See* Pet. Ex. 16 at 31; Resp. Ex. C at 4. Anatomically and pathologically, A.E.S. was otherwise normal.

The preponderant evidence shows a healthy baby who received multiple routine vaccinations in the morning, was whining and fussing as though in pain, not focusing, tracking, cuddling or feeding normally that afternoon. She was pronounced dead at 7:15 pm, eight hours after her vaccinations. The pathologists agreed that the only abnormalities on autopsy were a heavy brain and edema. They also agreed based on the evidence that this is not a SIDS case. When asked if the vaccinations contributed to A.E.S.'s death, Dr. Harris conceded, "I don't have an explanation for another diagnosis in this case." Tr. 242-43. There was no trauma and no evidence of neurological disease other than edema. Tr. 255-56. When asked if the DTaP vaccine can cause an acute encephalopathy, Dr. McCusker would only say that if one's definition of encephalopathy was cerebral edema leading to mortality, then "that has not been demonstrated in large studies." However, she agreed that the CDC cautions that encephalopathy following acellular pertussis vaccine is a contraindication to additional DTaP vaccines. Tr. 312.

Dr. Shuman testified that the signs of an encephalopathy in an infant A.E.S.'s age are limited and difficult to assess due to an infant's behavioral repertoire at that stage of development. *See* Tr. 129, 140-41, 163. However, the behaviors that are the within the repertoire of an 11-week-old that were demonstrated by A.E.S.—irritability, inability to self-soothe, not cuddling, not tracking or making eye contact, and sleeping more—were indicative of an altered state and decreased level of consciousness in the afternoon following her vaccinations sufficient to satisfy the Table requirements for an encephalopathy.[53] Therefore, I find that A.E.S. suffered from a Table encephalopathic event with cerebral edema following the receipt of multiple vaccinations that resulted in her death.

B. In the alternative, the vaccinations received by A.E.S. caused cerebral edema, encephalopathy, and death.

The legislative scheme that created Table injuries established a presumption of causation that alleviates the need for an actual causation determination. Having determined that A.E.S. suffered a Table encephalopathy, a causation analysis is unnecessary, but to be thorough, the off-Table causation-in-fact claim will be addressed as well.

1. *Althen* Prong I: Petitioners Have Provided a Reputable Medical Theory.

Vaccines can cause encephalopathy. The Institute of Medicine has written extensively about the relationship between pertussis and encephalopathy, concluding that the "evidence is

[53] As discussed further below regarding Prong I, Dr. Gershwin opined that, though rare, pro-inflammatory cytokines released in response to vaccination can cross the BBB, causing an inflammatory process affecting the brain and causing cerebral edema. Tr. 205-07. In *Nuttall*, Special Master Hastings concluded that there was no definition of encephalitis in the 2015 QAI and special masters accordingly need to apply the ordinary meaning of the term, which simply means any inflammation of the brain. *Nuttall v. Sec'y of Health & Human Servs.*, No. 07-0810V, 2015 WL 691272 (Fed. Cl. Spec. Mstr. Jan. 20, 2015), *aff'd*, 122 Fed. Cl. 821 (2015), *aff'd*, 640 F. App'x 996 (Fed. Cir. 2016). While there was no claim of encephalitis in the instant matter, it was undisputed that there was swelling of the brain. The interpretation of encephalitis in *Nuttall* creates the hypothetical possibility that an alternative avenue exists whereby petitioners here could be eligible for a Table claim irrespective of the requirement of 24 hours of reduced consciousness.

consistent with a causal relation between DPT vaccine and acute encephalopathy." Pet. Ex. 101[54] at 1; *see also* Pet. Ex. 19[55]; Pet. Ex. 20[56]; Pet. Ex. 21[57]; Pet. Ex. 30[58]; Pet. Ex. 33[59]; Pet. Ex. 34[60]; Pet. Ex. 62[61]; Pet. Ex. 99.[62] The National Childhood Encephalopathy Study (NCES) reported on 1000 cases of serious neurological illnesses in early childhood and their relationship to vaccines containing pertussis. The results suggested that DPT immunization was associated with an increased risks of seizures and encephalopathy within 7 days. Pet. Ex. 60 at 1, 4[63]; *see also* Pet. Ex. 59.[64]

The foregoing studies address the whole cell DTP, not the currently used acellular DTP, which has also been found to have adverse reactions, "[t]here are just fewer reactions to DTaP than to whole cell DTP." *Johnson v. Sec'y of Health & Hum. Servs.*, No. 07-138V, 2010 WL 3291932 at *15 (Fed. Cl. Spec. Mstr. July 30, 2010); *see also* Pet. Ex. 16 at 19. *Zielinski* studied the rate of systemic adverse reactions to whole cell DTP when compared with acellular DTP and found that systemic adverse reactions occurred after receipt of either vaccine, but twice as often with receipt of whole cell DTP. Pet. Ex. 100.[65]

Several vaccine cases have addressed the distinction between the DTP and DTaP vaccine formulations, concluding that the epidemiological findings relating to the safety of DTP vaccines cannot be transferred to the DTaP. *See, e.g.*, *Sharpe v. Sec'y of Health & Human Servs.*, No. 14-65V, 2018 WL 7625360, at *31-32 (Fed. Cl. Spec. Mstr. Nov. 5, 2018*); Taylor v. Sec'y of Health & Human Servs.*, No. 05-1133V, 2012 WL 4829293, at *30 (Fed. Cl. Spec. Mstr. Sept. 20, 2012); *Holmes v. Sec'y of Health & Human Servs.*, No. 08-185V, 2011 WL 2600612, at *20 (Fed. Cl. Spec. Mstr. Apr. 26, 2011); *Simon v. Sec'y of Health & Human Servs.*, No. 05-941V, 2007 WL 1772062, at *7 (Fed. Cl. Spec. Mstr. June 1, 2007); *Grace v. Sec'y of Health & Human Servs.*, No. 04-[redacted], 2006 WL 3499511, at *9 (Fed. Cl. Spec. Mstr. Nov. 30, 2006).

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[54] INST. OF MED., *Adverse Effects of Pertussis and Rubella Vaccines* 86 (Christopher P. Howson et al. eds., 1991), filed as "Pet. Ex. 101."
[55] Dolgopol, *supra* note 50.
[56] J. H. Menkes & M. Kinsbourne, *Workshop on Neurologic Complications of Pertussis and Pertussis Vaccination*, 21 NEUROPEDIATRICS 171 (1990), filed as "Pet. Ex. 20."
[57] B. A. Halperin et al., *Kinetics of the Antibody Response to Tetanus-Diphtheria-Acellular Pertussis Vaccine in Women of Childbearing Age and Postpartum Women*, 53 CLINICAL INFECTIOUS DISEASES 885 (2011), filed as "Pet. Ex. 21."
[58] *Pediarix Highlights of Prescribing Information*, GlaxoSmithKline, filed as "Pet. Ex. 30."
[59] CDC, *Surveillance for Safety After Immunization: Vaccine Adverse Event Reporting System (VAERS)—United States 1991-2001*, Morbidity & Mortality Weekly Report (2003), filed as "Pet. Ex. 33."
[60] Erick Sell & Berge A. Minassian, *Demystifying vaccination-associated encephalopathy*, 5 NEUROLOGY 465 (2006), filed as "Pet. Ex. 34."
[61] Steinman et al., *supra* note 13.
[62] CDC, *Pertussis Vaccination: Use of Acellular Pertussis Vaccines Among Infants and Young Children Recommendations of the Advisory Committee on Immunization Practices (ACIP)*, Morbidity & Mortality Weekly Report (1997), filed as "Pet. Ex. 99."
[63] D. L. Miller et al., *Pertussis immunization and serious acute neurological illness in children*, 282 BRITISH MED. J. 1595 (1981), filed as "Pet. Ex. 60."
[64] Nicola Madge et al., *The National Childhood Encephalopathy Study: A 10-Year Follow-Up*, 68 DEVELOPMENTAL MED. & CHILD NEUROLOGY 1 (1993), filed as "Pet. Ex. 59."
[65] Andrzej Zielinksi & Magdalena Rosinska, *Comparison of Adverse Effects Following Immunization with Vaccine Containing Whole-Cell vs. Acellular Pertussis Components*, 92 PRZEGLĄD EPIDEMIOLOGICZNY 589 (2008), filed as "Pet. Ex. 100."

However, literature demonstrates that encephalopathy is a known risk of DTaP vaccination. In the DTaP Vaccine Information Statement ("VIS"), the CDC cautions that any child who suffered a brain or nervous system disease within seven days of a dose of DTaP should not get another dose. Pet. Ex. 98.[66] The Morbidity and Mortality Weekly Report distributed by the CDC provides that if encephalopathy occurs within seven days of administration of DTaP or DTP, subsequent vaccination with DTaP or DTP is contraindicated. Pet. Ex. 99 at 17-18.[67] The package insert for the DTaP vaccine warns that "[e]ncephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) within 7 days of administration of a previous dose of a pertussis-containing vaccine that is not attributable to another identifiable cause is a contraindication to administration of any pertussis-containing vaccine, including PEDIARIX." Pet. Ex. 30 at 4.[68] Thus, sufficient medical literature demonstrates, and the CDC accepts, that DTaP can cause encephalopathy.

Further, the package inserts for both the DTaP and Prevnar 13 vaccines contain warnings of apnea in premature infants. Pet. Ex. 16 at 21. Prevnar 13 is a conjugate vaccine which contains Diphtheria CRM protein. The package insert states that data is insufficient to assess the effects of concomitant administration of Prevnar 13 with HPV, MCV4, tetanus toxoid, and Tdap. Pet. Ex. 35 at 21, 24-25.[69] The pneumococcal polysaccharides in the Prevnar 13 vaccine, though not as toxic as pertussis toxin, have been linked to cardiac-mediated cyanosis, vascular pallor, respiratory-mediated apnea, and nervous system-mediated hypotonia. *Id*. at 20-21; Pet. Ex. 16 at 28. Table 4 of the package insert shows that 80% of infants vaccinated with Prevnar 13 suffer irritability, 70% at two months sleep too much, and 50% had diminished appetite. Pet. Ex. 16 at 28 (citing Pet. Ex. 35 at 9).

According to Drs. Shuman and Gershwin, Pediarix, Hib, PCV13, and RotaTeq vaccinations can, individually or in combination, produce cerebral edema, axial herniation, and death through the circulation of cytokines to the brain. Pet. Ex. 16; Pet. Ex. 63; Pet. Ex. 65[70]; Pet. Ex. 66[71]; Pet. Ex. 92; Pet. Ex. 97.

While the experts did not agree that A.E.S.'s vaccines were the cause of her death, they did agree about the body's immune response to receiving vaccinations. According to Dr. Shuman, vaccines can affect the brain through immunological processes that can be destructive. Pet. Ex. 92 at 4. Vaccines elicit cytokines necessary in inducing immunological response. The DTaP, Hib, and PCV vaccines are proven to stimulate the production and circulation of proinflammatory cytokines including IL-1β, IL-6, and TNF-α. IL-1β stimulates macrophage production, T-cell production, and can cause fever. IL-6 stimulates T and B cells and can cause acute phase reactions such as inflammation and fever. TNF-α stimulates formed macrophages to make more cytokines (in a positive feedback loop) and inflammatory invasion by monocytes, which then transform into more macrophages, and activate endothelial cells. Pet. Ex. 92 at 4. The increase of vascular permeability causes separation of the endothelial cell lining of the blood vessel walls, leading to the leaking of

[66] CDC, *Vaccine Information Statement: DTaP Vaccine* (2007), filed as "Pet. Ex. 98."
[67] CDC, *supra* note 62.
[68] GlaxoSmithKline, *supra* note 58.
[69] Pfizer, *supra* note 15.
[70] Kashiwagi et al., *supra* note 21.
[71] Pan et al., *supra* note 26.

fluid and protein from the blood which accumulates in the tissue and causes swelling or edema. *Id*. These changes to the endothelium result in inflammation known as endothelial activation. TNF-α is a potent cytokine activator of endothelial cells.[72] *Id.* at 5. Dr. Shuman added that the production of IL-1β is "provoked by vaccines more in the first year of life than later in life" and is "significantly more provoked by multiple vaccines than it is by single vaccines." *Id*.

Dr. Gershwin explained that the innate immune system produces proinflammatory cytokines and chemokines in response to infections and vaccines which can cause or prevent inflammation. These immune cells enable communication between the innate and adaptive immune systems, as well as between the innate cells and other tissues of the body. Tr. 182-85. *Kashiwagi* illustrated the various cytokines present in the body after vaccination. Tr. 191-92, 201; Pet. Ex. 65.[73] Vaccines produce cytokines and chemokines at the vaccination site—which is why there is swelling at the site—which drain into the lymph nodes, circulate around the body, and can cross the blood brain barrier, producing biologic effect. Adaptive cells then present and build antibodies and cytotoxic T-cells. Tr. 185-88; Pet. Ex. 104[74] at 4.

Acknowledging that no literature has addressed which proinflammatory cytokines produced in the blood after vaccination can cross the BBB, Dr. Gershwin believes it would be variants such as IL-1 and IL-6. Studies do show that influenza infection produces proinflammatory cytokines that can cause encephalopathy, and Reyes Syndrome produces proinflammatory cytokines that causes swelling in the body. Proinflammatory cytokines produce swelling and edema anywhere in the body, so there is no reason to believe the brain after vaccination is an exception. Tr. 205-07. Dr. Gershwin added this is an extremely rare event, making it unlikely to be studied, but it happened to A.E.S. and rare events are the basis for the vaccine program. Tr. 205.

Dr. McCusker similarly described an initial cascade of inflammation during an innate immune response at the site of infection or trauma, but argued it is transient and tightly regulated with most cytokine events occurring locally without generating a systemic effect. Resp. Ex. A at 6; Resp. Ex. E at 2. She acknowledged that proinflammatory cytokines can cause local pain, redness, systemic fever, and malaise, which is the body's way of stopping replication of the pathogen and increasing basal metabolic rate to activate the adaptive immune system to generate immunological memory. Resp. Ex. A at 6. She added, however, the effects are limited and usually resolve when the acute infection is eliminated or when the adaptive immune response neutralizes the pathogen. *Id*.

According to Dr. McCusker, the cytokines produced by vaccination are far less than those produced by natural infection and are therefore not sufficient for the development of brain edema. Resp. Ex. A at 6; Resp. Ex. E at 3; Resp. Ex. E, Tab 4.[75] Further, vaccines and infections in general

[72] Dr. McCusker relied on *Hingorani* to show that the timing associated with an increase of inflammatory cytokines was within hours of vaccination and to conclude that A.E.S. could not have had signs of encephalopathy. *See* Resp. Ex. E at 3; Tr. 281. However, *Hingorani* actually discusses how the inflammatory process caused by the increase in cytokines can disrupt vascular homeostasis and arterial circulation. The authors found an association between even mild systemic inflammatory response to cytokines and profound suppression of endothelium-dependent relaxation in circulation thought to be associated with increased cardiovascular risk. Resp. Ex. E, Tab 3 at 3.
[73] Kashiwagi et al., *supra* note 21.
[74] Hervé et al., *supra* note 25.
[75] Kashiwagi et al., *supra* note 21.

are not known to disrupt the BBB. Resp. Ex. E at 5-6; Pet. Ex. 85.[76] She relied on *Suntharalingam* to show that even after a T-cell immunomodulatory agent is injected into adults, creating a "cytokine storm" or rapid onset of systemic inflammatory response syndrome (SIRS), no one developed signs of encephalopathy or significant brain edema. Resp. Ex. E at 3; Resp. Ex. E, Tab 5.[77] However, this study involved adults, not infants.

Dr. McCusker explained that the brain contains microglial cells which release cytokines under baseline conditions and increase the release of IL-1 and IL-6 to maintain homeostasis when exposed to stressors such as acute brain injury and neurodegeneration. Resp. Ex. E at 2, 4; *see* Resp. Ex. E, Tab 6[78], Resp. Ex. E, Tab 7.[79] She acknowledged that an overexpression of cytokines in the CNS can be detrimental to the brain and that cytokines can "diffuse across the BBB" through receptors or through the vagus nerve but contends this does not mean cytokines enter the CNS, only that the brain gets the message of their presence. Tr. 286-87; Resp. Ex. E at 4; Resp. Ex. E, Tab 11.[80]

Succinctly, Dr. McCusker stated that the literature relied on by petitioners' experts does not support peripheral cytokine release after vaccination being capable of generating life-ending brain edema, and even a cytokine storm cannot cause disruption of the BBB causing death. Resp. Ex. E at 6; Resp. Ex. A, Tab 13[81] at 5.

The literature does demonstrate that encephalopathy is a known risk of DTaP vaccination and that both DTaP and Prevnar 13 vaccines have been associated with apnea in premature infants. Pet. Ex. 98[82]; Pet. Ex. 99 at 17-18[83]; Pet. Ex. 30[84]; Pet. Ex. 16 at 21. The Prevnar 13 vaccine has also been linked to cardiac-mediated cyanosis, vascular pallor, respiratory mediated apnea, and nervous system-mediated hypotonia. Pet. Ex. 16 at 28. The additional literature filed by Dr. McCusker after the hearing provides that the data is insufficient to assess the effects of concomitant administration of Prevnar 13 with HPV, MCV4, tetanus toxoid, and Tdap. Pet. Ex. 35 at 21, 24-25[85]; Resp. Ex. F. A.E.S. received a hexavalent vaccine containing DTaP/IPV/HepB, Hib, Prevnar 13 (PCV13), and RotaTeq vaccinations on the day of her death.

Petitioners have presented preponderant evidence to show that on rare occasions, the release of proinflammatory cytokines in response to vaccines can cause a systemic inflammatory response to an antigen load that can overwhelm immunomodulatory controls, resulting in encephalopathy and cerebral edema. Petitioners have satisfied Prong I.

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[76] William A. Banks & Abba J. Kastin, *Review: Interactions Between the Blood-Brain Barrier and Endogenous Peptides: Emerging Clinical Implications*, 295 AM. J. MED. SCI. 459 (1996), filed as "Pet. Ex. 85."
[77] Suntharalingam, *supra* note 32.
[78] Ron-Harel et al., *supra* note 33.
[79] Moidunney et al., *supra* note 34.
[80] Quan, *supra* note 35.
[81] Rafael Ponce, *Adverse Consequences of Immunostimulation*, 5 J. IMMUNOTOXICOLOGY 33 (2008), filed as "Resp. Ex. A, Tab 13."
[82] CDC, *supra* note 66.
[83] CDC, *supra* note 62.
[84] GlaxoSmithKline, *supra* note 58.
[85] Pfizer, *supra* note 15.

2. *Althen* Prong II: Petitioners Have Provided a Logical Sequence of Cause and Effect

The autopsy findings in this case were unremarkable, except for a brain weight of 595 grams and cerebral edema. Pet. Ex. 3 at 3. The medical examiner concluded that the cause and manner of death were best classified as "undetermined", and the findings were consistent with Sudden Unexpected Infant Death (SUID). Pet. Ex. 3 at 4.

As the person who conducted the autopsy, Dr. Barnhart's views are entitled to some deference. *Nordwall v. Sec'y of Health & Human Servs.*, 83 Fed. Cl. 477, 488 (2008). However, findings of a treating doctor are not sacrosanct. *Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 745 n.67 (2009).

There is little dispute between the pathologist who performed the autopsy and those hired in this case about the autopsy findings. All agreed that there was heavy brain, brain edema, and the cause of death was "undetermined" based on the history of no prior illness, no foul play, and no pathological findings to explain her death.

Dr. Harris agreed A.E.S.'s brain was heavier than expected in a child her age and the swelling or edema was "an abnormal finding or a pathological finding. It's not normal. But we don't know what the cause of that swelling is in many cases of infant death, sadly." Tr. 231-32. Further, he stated that the brain weight was a "pathological abnormality." Tr. 250-51. The congestion in the organs was also a pathological abnormality. Tr. 251; Pet. Ex. 3 at 3-4.

Dr. Shuman opined the heavy brain was consistent with cerebral edema caused by the multiple vaccines A.E.S. received at one time constituting a "profound immunologic challenge." Pet. Ex. 16 at 18, 31. The cytokines generated from the vaccines circulated to A.E.S.'s brain, disrupted the cerebral blood brain barrier, and produced severe rapid cerebral edema causing death by axial herniation. A.E.S. suffered a malignant form of cerebral edema which was widespread, rapidly progressive, and lethal within 6-8 hours of vaccination. *Id*. at 36-37.

Dr. Shuman referred to the autopsy photographs showing swelling at the injection sites on A.E.S.'s thighs, indicating an inflammatory reaction of the local tissue, necessary for cytokine release and spread by circulation. Tr. 161; Pet. Ex. 18 at 2. Dr. Shuman stated that the vascular system is very reactive to cytokines and the cytokines released and activated by adjuvanted vaccines, including IL-1, IL-6, tumor necrosis factor, C55 complement, and some prostaglandins, are extraordinarily and systemically vasoreactive on the brain and pulmonary vasculatures. This is demonstrated by their producing cerebral and pulmonary edema, third-spacing, hypovolemic hypotension, shock, and progressive encephalopathic death, as seen with A.E.S. Tr. 162-63.

Dr. Shuman explained that the pertussis toxin in the DTaP vaccine targets the brain, clinically and experimentally producing hypotonic spells, systemic and neurologic collapse, coma, and seizures. Pet. Ex. 16 at 28; Pet. Ex. 62.[86] The pneumococcal polysaccharides in the Prevnar 13 vaccine have been linked to cardiac mediated-cyanosis, vascular (cardiac)-mediated pallor, respiratory-mediated apnea, and nervous system-mediated hypotonia. *Id*. at 28. The package insert

[86] Steinman et al., *supra* note 13.

at Table 4 shows that of infants from two to 12 months of age vaccinated with Prevnar 13, 80% suffer irritability, 70% of two-month-old infants slept too much, and 50% had diminished appetite. Pet. Ex. 16 at 28; Pet. Ex. 35[87] at 9. These "misbehaviors" show disrupted brain function in infants, which become less frequent in older infants, because "[t]he CNS of the younger infant is most susceptible to neural toxicity." Pet. Ex. 16 at 28.

Dr. Shuman described the weight of A.E.S.'s brain as a "robust sign of cerebral edema", with objective findings on autopsy including a full and flattened brain "obviously under pressure," a brain weight at least two standard deviations above the mean for a 10-week-old female, and the absence of inflammation or other obvious cause of death in the limited samples of the brain taken. Tr. 133-140, 142; Pet. Ex. 92 at 1-2; Pet. Ex. 47[88]; Pet. Ex. 48[89]; Pet. Ex. 49.[90] He explained that when the brain swells, it takes up more space and the pressure within the skull increases. The brain is somewhat like fluid, and it shifts compartments and cuts off vessels between the compartments when the volume and pressure increase. When brain pushes against brain, the pressure pushes downward on the brainstem, which causes bradycardia and interferes with functions such as focus, gaze, tracking, sucking, and swallowing. Tr. 133-36; Pet. Ex. 16 at 27. Once the cerebral edema causes axial herniation and the brainstem is impaired, death ensues soon after. A.E.S. "was not resuscitable because the brainstem could not resume control of the viscera" and she suffered multiorgan failure and death soon after. Pet. Ex. 16 at 36-37.

Dr. Harris agreed A.E.S.'s brain was heavy with swelling and mild edema, but explained herniation is very difficult to assess on an infant brain at autopsy. Resp. Ex. C at 6. However, there were insufficient findings of hypoxia-ischemia or infection to explain the edema on the brain. *Id*. He disagreed that *Dolgopol* applied in this case because it discussed the neuropathological changes in infants who died from pertussis infection encephalopathy with autopsies showing variable edema, hemorrhages, and neurodegeneration, while A.E.S. had mild edema with no hemorrhages, neurodegenerative changes, or signs of cell death on the brain tissue. *Id*.; Pet. Ex. 19.[91] Dr. Harris admitted that while he did not see signs of hypoxia or ischemia on the autopsy slides, he could not dispute that the edema could be an early sign of a hypoxic or ischemic event. Tr. 235.

Dr. Harris concurred that the gelatinous nature of the brain tissue makes it more challenging to observe herniation on autopsy and noted that the medical examiner did not mention other signs of herniation such as internal and external hemorrhage, but he added that he did not know the level of competence of the medical examiner to recognize early herniation in an infant. Tr. 236-37. He stated that key sections of the brain, including the brainstem, were not sampled and "…not having those makes it very difficult, unfortunately, to say whether or not there was herniation in this case." Tr. 236-37. However, he could not "rule it out or rule it in" from a pathological standpoint. Tr. 237, 256. When pressed on the issue, he expressed the challenges in assessing brainstem herniation without imaging studies or a full examination of the brain. He explained that even with the degree of swelling on the surface of the brain, the overall weight of the brain, and what he heard clinically, he could not say that a herniation occurred. Tr. 238-39. However, he also could not rule in or out

[87] Pfizer, *supra* note 15.
[88] Kayser et al., *supra* note 18.
[89] Schulz et al., *supra* note 19.
[90] Coppoletta & Wolbach, *supra* note 20.
[91] Dolgopol, *supra* note 50.

inflammation in other areas of the brain because of the scant amount of brain tissue sampled. Tr. 239. He stated he too would have concluded the cause of death was undetermined based on the pathological findings and mild cerebral edema had he been the medical examiner. Tr. 240.

Drs. Shuman and McCusker disagreed about the congestion of the organs and the frothing of the lungs. Dr. McCusker stated it was from resuscitation efforts, while Dr. Shuman stated it was indicative of fluid transmuting across the vasculature in the pulmonary space, which similarly occurred in the brain vasculature, producing cerebral edema and causing A.E.S. to become hypovolemic and hypotensive. This was all related to the process of the cytokines. Tr. 172, 175-77; Pet. Ex. 3 at 3-4. Dr. Harris argued that pulmonary edema and congestion are common and non-specific findings in all age groups on autopsy. Resp. Ex. C at 5.

Dr. Shuman discussed the repertoire of encephalopathic behaviors in an infant at A.E.S.'s age and noted A.E.S.'s irritability, inability to soothe, and not having a normal gaze or social response as described by her parents. Tr. 129-31, 140-46. He added A.E.S. was in a decerebrate posture when found, a sign of axial herniation and encephalopathy. Tr. 140. Based on the evidence, he concluded that A.E.S. was encephalopathic with a decreased level of consciousness as indicated by decreased or absent responses to her environment, and clinical signs of absent eye contact and absent or inconsistent responses to external stimuli. These behaviors correlate with significant progressive cerebral edema, axial gradation, and compression of function of the brain tissue. Tr. 163. The process of A.E.S.'s encephalopathy completed at some time between the time when her mother left for work and before her father found her in the bassinet. Tr. 141-42.

Dr. McCusker disagreed, stating that A.E.S. showed no clinical signs of immune activation, acute cerebral edema or increased intracranial pressure in the 90 minutes prior to being found unresponsive. Tr. 298-99, 306; Resp. Ex. E at 7. In her experience, an encephalopathic child is not quiet with "soft behavioral changes" but is in pain, won't eat, is nauseous, vomiting, and has a severe headache. Tr. 299.

As expected, petitioner's experts concluded that the multiple vaccines received by A.E.S. six to eight hours prior to her death were the cause of her death. Respondent's experts disagreed. However, Dr. Harris was candid in his inability to rule in or out the conclusions reached by Dr. Shuman. Further, when asked if he could definitively say that A.E.S.'s death was not the result of the vaccines, he stated, "Yeah, I base my opinion, though, on the medical literature and the fact that the timing of this autopsy or of the vaccination could not have been an anaphylactic reaction. And I'm not aware of any literature to suggest that vaccination other than anaphylaxis could lead to a death like this." Tr. 242. However, "I don't have an explanation for another diagnosis in this case." Tr. 242-43. There was no trauma and no evidence of neurological disease other than edema. Tr. 255-56.

A.E.S. did not live long enough to display all the characteristic behaviors typically associated with encephalopathy in an infant, but her behavior in the hours following the vaccinations followed by an unresponsive state and subsequent death and autopsy findings satisfy Prong II.

3. *Althen* Prong III: Petitioners Have Demonstrated a Proximal Temporal Relationship

Dr. Gershwin opined that the temporal association between the vaccines A.E.S. received and her encephalopathy and death is "consistent." Tr. 200. The rapid onset of A.E.S.'s encephalopathy would imply a cytokine-mediated event because something that occurred so rapidly would be immunological. Tr. 199.

Dr. Harris stated that changes on the brain from hypoxia-ischemia typically take at least six hours and agreed that the edema seen on the autopsy could have been an early sign of hypoxia/ischemia. However, he "could not make that judgment without seeing multiple areas of the brain." Tr. 233-34.

A.E.S. received the vaccinations at approximately 11:00 am on December 13, 2016. Pet. Ex. 2 at 16-19; Pet. Ex. 7 at 9. She was found unresponsive in her bassinet at approximately 6:15 pm that day, seven hours after her vaccinations. She was pronounced dead at approximately 7:15 pm. Pet. Ex. 7 at 1, 7; Pet. Ex. 5 at 11, 57-58. Dr. Shuman explained that the behaviors Ms. Sims described - a distant look in A.E.S.'s eyes, not making eye contact, whimpering, and acting "the way you would if you had a headache," all abnormal for her - were indicative of the distress A.E.S. was experiencing. Tr. 22-23, 40, 142-46; Pet. Ex. 135 at 2. The ER record documents "cardiac arrest and sepsis with anaphylaxis. Pet. Ex. 5 at 11.

While Dr. McCusker disagreed that A.E.S. showed any clinical signs of immune activation, acute cerebral edema, or increased intracranial pressure, she did state that it takes at least three hours for cytokines to release after vaccination. Tr. 280-81, 298-99, 306; Resp Ex. E, Tab 4[92]; Resp. Ex. E at 7. A.E.S. was found unresponsive at 6:15 pm, approximately seven hours after vaccination and well outside the time at which cytokines are released into the muscle as stated by Dr. McCusker based on *Kashiwagi*.[93] Further, while the subtle changes in A.E.S.'s regular behavior in the afternoon following her receipt of the subject vaccinations were described by her parents, it is unknown how A.E.S.'s behavior changed and evolved or what occurred from the time she was laid down in her bassinet around 5 pm until was found unresponsive around 6:15 pm. The literature supports that cytokine release could have occurred as early as three hours post-vaccination, accounting for her early behavior changes. Accordingly, petitioners have presented preponderant evidence to satisfy Prong III.

C. Burden Shifting: Alternative Cause

Petitioners addressed the issue of alternative cause, submitting that there was no evidence of infection on gross or microscopic examination or cultures post-mortem. Pet. Ex. 16 at 24. There was no indication of predisposing chronic stress on autopsy. *Id*. at 28. The features of the home environment, the sleeping site, its materials, and the position of A.E.S.'s body were inconsistent with SIDS. *Id*. Cerebral edema is not a feature of SIDS, but it was a marked feature on the autopsy in this case. Pulmonary edema and congestive heart failure are not features of SIDS, but both were

[92] Kashiwagi et al., *supra* note 21.
[93] *Id*.

present when A.E.S. was brought to the ER. Pet. Ex. 16 at 36. This case does not fit the classic profile of SIDS. *Id*. at 26. Dr. Harris agreed that SIDS cannot be invoked in this case. Tr. 253-54.

Respondent submits that a mere showing of temporal relationship between vaccines and injury "nor a simplistic elimination of other potential causes of the injury suffices without more, to meet the burden of showing actual causation." Resp. Post-H Brief at 25 (quoting *Althen*, 418 F. 3d at 1278). This holds true for respondent as well. The burden shifts to respondent to show an alternative cause once petitioners have satisfied *Althen*.

Dr. McCusker submits that Long QT Syndrome is "one plausible explanation for [A.E.S.'s] clinical picture and death", because her sibling born after her death had Long QT after birth and was sent home from the hospital with an apnea monitor. Resp. Ex. A at 7; Resp. Ex. E at 7; Pet. Ex. 15 at 5. Dr. McCusker submitted that Long QT and channelopathies "have been implicated in up to 20% of sudden infant deaths," and the fact that A.E.S.'s sibling had Long QT early in life "raises the possibility that A.E.S. may also have had prolonged QT." Resp. Ex. A at 7; Resp. Ex. E at 7. However, genetic studies were never done, and an EKG done at a follow-up examination after the birth of A.E.S.'s sibling was normal, and petitioners were assured the baby was fine. Tr. 36-38.

Dr. McCusker's alternative explanation for the death of A.E.S is unsupported, speculative, and/or conclusory in nature. In order to prove alternative causation, respondent must "present sufficient evidence to prove that the alternative factor was the sole substantial factor in bringing about the injury." *Deribeaux*, 717 F.3d at 1367. The Vaccine Act limits the scope of unrelated factors by excluding any "idiopathic, unexplained, unknown, hypothetical or undocumentable cause, factor, injury, illness or condition." § 13(a)(2)(A). "In other words, alternative causes that are 'idiopathic, unexplained, unknown, hypothetical or undocumentable' cannot overcome a petitioner's prima facie case." *Doe*, 601 F.3d at 1357 (quoting § 13(a)(2)(A)).

In the 11 weeks since her birth and prior to her death, A.E.S. slept in her parents' room and showed no signs of sleep apnea. Further, although A.E.S.'s sibling born after her death demonstrated concerns for Long QT Syndrome after birth, in Dr. McCusker's own words, she described Long QT as only a "plausible" explanation for A.E.S.'s death and conceded that genetic studies were not done. It is well-established that a plausible or possible theory is insufficient to prove that an injury occurred. *Moberly*, 592 F.3d at 1322; *Boatmon v. Sec'y of Health & Human Servs.*, 941 F.3d 1351, 1360 (Fed. Cir. 2019).

Accordingly, because petitioners have carried their burden in establishing a prima facie case of causation and respondent has failed to establish an alternative cause that is more than speculative, petitioners are entitled to compensation.

VII. Conclusion

Upon careful evaluation of all the evidence submitted in this matter—the medical records, the testimony of petitioners and the experts, and the medical literature—I find that petitioners have shown that they are entitled to compensation under the Vaccine Act. Accordingly, this matter shall proceed to damages.

IT IS SO ORDERED.

s/ Mindy Michaels Roth
Mindy Michaels Roth
Special Master