In the United Stated Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 99-212V
(Filed: October 29, 2008)

JOHN DOE/11 and JANE DOE/11, as Representatives of the Estate of CHILD DOE/11, Deceased, Petitioners, v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	)	Remand; Allegations of Heavy Brain Weight, Encephalopathy, and Fatal "Cytokine Storm" after Hepatitis B Vaccination; Petitioners Fail to Satisfy Burden of Proof under Althen

Richard Gage, Cheyenne, WY, for petitioner.

Glenn A. MacLeod, with whom were Jeffrey S. Bucholtz, Acting Assistant Attorney General, Timothy P. Garren, Director, Mark W. Rogers, Deputy Director, and Gabrielle M. Fielding, Assistant Director, Department of Justice, Civil Division, Torts Branch, Washington, DC, for respondent.

DECISION ON REMAND[1]

Campbell-Smith, Special Master

[1] Vaccine Rule 18(b) provides that all decisions of the special masters will be made available to the public unless an issued decision contains trade secrets or commercial or financial information that is privileged or confidential, or the decision contains medical or similar information, the disclosure of which clearly would constitute an unwarranted invasion of privacy. Special masters afford the parties a fourteen day time period from the issuance of a decision to move for the redaction of privileged or confidential information before the document's public disclosure.

On April 8, 1999, petitioners, John Doe/11 and Jane Doe/11, as representatives of the Estate of Child Doe/11, filed a petition pursuant to the National Vaccine Injury Compensation Program[2] (the Act or the Program). Petitioners alleged that their daughter, a seven week-old, died during the evening of December 21, 1994, as a result of receiving a hepatitis B vaccination earlier that afternoon. Petitioners relied on a causation in fact theory, specifically, that the administered hepatitis B vaccination triggered an adverse reaction known as a "cytokine storm," which caused cerebral edema and led to her death four and a half hours later.

During a recorded entitlement hearing, the undersigned heard testimony from petitioners.[3] The testimony of petitioners concerning Child Doe/11's state after her receipt of the hepatitis B vaccination and the circumstances surrounding her death provided additional factual details for consideration that were not otherwise reflected in the record. The undersigned also heard the testimony of the parties' respective experts during the recorded hearing. Both parties presented an immunologist and a pathologist to testify on the causation issue.

After the parties submitted post-hearing briefing, the undersigned issued a decision finding that petitioners were not entitled to compensation. Petitioners appealed the decision. On July 31, 2008, an Opinion and Order of the United States Court of Federal Claims vacated the issued decision and remanded the case to the undersigned to evaluate petitioners' claim by allocating the proper burden of proof to petitioners and by addressing explicitly and separately each of the three prongs of the causation test articulated by the Federal Circuit in Althen v. Secretary of the Department of Health and Human Services, 418 F.3d 1274, 1278 (Fed. Cir. 2005).

Because petitioners have failed to satisfy their burden of proof on prongs two and three of the Althen standard, they are not entitled to compensation. Before turning to the analysis of petitioners' claim, however, the undersigned first reviews the factual record.

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[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C.A. § 300aa-10-§ 300aa-34 (West 1991 & Supp. 2002) (Vaccine Act or the Act). All citations in this decision to individual sections of the Vaccine Act are to 42 U.S.C.A. § 300aa.

[3] Jane Doe/11 was sequestered during John Doe/11's testimony.

I. The Factual Record[4]

Although Jane Doe/11's medical records identified her pregnancy with Child Doe/11 as an "at risk" one, her pregnancy and delivery at forty-one weeks appears to have been uneventful. See Petitioners' Exhibit (Ps' Ex.) 1 at 1-4; Ps' Ex. 2 at 8. Child Doe/11 was born on October 31, 1994, weighing 9 lbs 10 ozs. Joint Stipulation ¶ 1; Ps' Ex. 2 at 2. Child Doe/11's pediatric growth chart indicates that she was in the ninety-fifth percentile for weight at her birth. Ps' Ex. 3 at 7. At birth, she measured twenty inches long, and her pediatric growth chart indicates that she was in the fiftieth percentile for length.[5] Id. at 7. Her Apgar scores at birth were 7 and 9.[6] Joint Stipulation ¶ 2. Her newborn examination was normal. Id. On the date of her birth, she received her first hepatitis B vaccination. Id. ¶ 3. She was discharged from the hospital on November 1, 1994, the day following her birth. Id.

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[4] Included in the parties' pre-hearing submissions are certain "[a]greed [u]pon [f]acts," which were proposed by respondent and agreed to by petitioners, and were set forth in the Joint Stipulation filed on October 4, 2006. These facts are cited as Joint Stipulation (Joint Stipulation of Uncontested Fact filed 10/4/06). The undersigned cites to the medical and police records filed in this case and the hearing transcript for all other facts.

[5] This measurement, contained in an undated pediatric growth chart, is the one upon which petitioners' expert, Dr. Shane, relied during his testimony. Other filed medical records, including some of the birth records for Child Doe/11, indicate that her birth length was twenty-one and three-fourths inches. See, e.g., Ps' Ex. 2 at 3, 19. The undersigned addresses the issue of conflicting record notations regarding Child Doe/11's length at birth and at her two-month pediatric visit at Part III(B)(2)(a)(iii)(A) of this decision.

[6] An Apgar score is "a numerical expression of the condition of a newborn infant . . . , being the sum of points gained on assessment of the heart rate, respiratory effort, muscle tone, reflex irritability, and color." Dorland's Illustrated Medical Dictionary 1670 (30th ed. 2003). The Apgar score, developed in 1952 by anesthesiologist Virginia Apgar, "is a numerical expression of the condition of a newborn infant, usually determined 60 seconds after birth." Dorland's Illustrated Medical Dictionary 1670; The Apgar Score, http://www.babycenter.com/refcap/3074.html (November 19, 2007). The score reflects a combined numerical measurement of a newborn's appearance (color), pulse (heart rate), grimace (reflex irritability or responsiveness), activity (muscle tone), and respiration. Id.; see also Neil M. Davis, Medical Abbreviations 51 (12th ed. 2005). Each of these five indicators is assigned a number between zero and 2 (2 being the strongest rating), and the numbers are totaled to yield the Apgar score. A perfect score is 10. The Apgar Score, http://www.babycenter.com/refcap/3074.html (last visited November 19, 2007).

On November 9, 1994, nine days after Child Doe/11's birth, her pediatrician examined her and reported that she was developing appropriately. Ps' Ex. 3 at 1. The pediatrician's records indicate that he drained Child Doe/11's right eye during the office visit and subsequently treated both of her eyes with antibiotic eye drops. Id.

About six weeks later, on December 21, 1994, Child Doe/11 returned to the pediatrician's office for a well-child visit and for the receipt of her second hepatitis B vaccination. Id. at 3. Child Doe/11 was seven weeks old. She weighed 11 lbs. Id. at 3. Her pediatric growth chart indicates that she was in the ninetieth percentile for her weight during that visit. Id. at 7. Her head circumference was 39 cm. Id. at 3. Her pediatric growth chart indicates that she was in the ninetieth percentile for her head circumference during that visit. Id. at 6. Her length was recorded as twenty-one and a half inches. Id. at 7. Her pediatric growth chart indicates that she was in the fiftieth percentile for length. Id.

Her scheduled appointment was at half past one o'clock in the afternoon. Transcript of October 12, 2006 hearing (Tr.) at 11 (mother's testimony). She received her second hepatitis B vaccination at approximately two o'clock. Id. The vaccination was administered in Child Doe/11's thigh, and she cried in response. Id. at 36.

After Child Doe/11's appointment, the Doe family went Christmas shopping at the mall with Child Doe/11. Tr. at 11. According to John Doe/11, who testified that he carried Child Doe/11 in a transportable car seat during the family's shopping trip, Child Doe/11 slept the whole time the family shopped for holiday gifts. Tr. at 37. She did not feed during that time. See Tr. at 30-31, 37. Nor did she interact with the family while they shopped. See Tr. at 30-31, 37. John Doe/11 testified that he did not notice Child Doe/11 to have a fever or to have any abnormal jerking during the family's shopping trip. Tr. at 37-38. John Doe/11 also testified that Child Doe/11 did not cry at all between the time that she received her vaccination and several hours later when John Doe/11 noticed Child Doe/11 turning blue at home. Tr. at 38. Child Doe/11's pediatrician had informed the Does "that [the vaccination] would make Child Doe/11 drowsy." Tr. at 36-37.

To some extent, the testimony of Jane Doe/11 was not consistent with her husband's testimony. Jane Doe/11 testified that after the vaccination, Child Doe/11's affect was unusual, and that although Child Doe/11 was awake during the shopping trip, there was "[n]o crying. . . . She usually cries, and she wasn't even making a sound . . . ." Id. Jane Doe/11 testified that "[at] first we didn't notice [any reaction to the vaccination], but towards the end, when we were getting home . . . [Child Doe 11] wasn't drinking

from her bottle, which [was] very unusual . . . and she was very tired – lethargic."[7] Id. at 15.

Jane Doe/11's testimony that Child Doe/11did not feed was consistent with her husband's recollection. But, Jane Doe/11's testimony that Child Doe/11 was awake while shopping conflicted with the recollection of her husband John Doe/11. To the extent that Jane Doe/11's testimony indicated that Child Doe/11 remained awake during the family's shopping trip, the undersigned does not find the Does' testimony to have been inconsistent with each other. To the extent the Does' testimony conflicted on Child Doe's general state of wakefulness or sleepiness during the shopping trip, the undersigned credited John Doe 11's testimony that Child Doe/11 was sleepy as more likely to be accurate because he carried Child Doe/11 in her car seat during the family's outing. See Lampe v. Sec'y of Dept. of Health and Human Servs., 219 F.3d 1357, 1362 (Fed. Cir. 2000) (A special master's "assessments of the credibility of the witnesses" are "virtually unreviewable on appeal."); Bradley v. Sec'y of Dept. of Health and Human Servs., 991 F.2d 1570, 1575 (Fed. Cir. 1993) (A special master is afforded "broad discretion in determining credibility because [she] saw the witnesses and heard the testimony.").

After shopping, the family returned home around five o'clock that afternoon. Tr. at 12. Jane Doe/11 testified that the family "all laid down for a nap – me and the two boys laid in the bedroom, and [John Doe/11,] my husband, and [Child Doe/11] laid [down] outside on the couch." Id. at 12. Jane Doe/11 indicated that her husband "was laying down on the couch. [Child Doe/11] was right next to him, propped up on a pillow." Id. at 18, 19. Child Doe/11 "was face-up." Id. at 18.

John Doe/11 testified that he fell asleep beside Child Doe/11 between 5:30 and 6:00 p.m. Tr. at 32-33. It was his testimony at the hearing that he had placed Child Doe/ 11 next to himself, propped up on a pillow, on the family's futon on her back with her face up. See id. at 31-33. John Doe/11 testified that he positioned Child Doe 11/ next to him "to, like, you know, cuddle with me on the futon, and I watched news, you know, until I fell asleep." Id. at 31. As John Doe/11 described how he positioned his daughter next to him, he gestured with his hands indicating that Child Doe/11 was lying on a pillow to his right, and he explained that "[w]e were both laying on a pillow and the futon is – it's like a mattress that slopes – and we're just kind of laying on a pillow and she's like even with me." Id. at 40.

When John Doe/11 awakened about 30 minutes after falling asleep, he noticed that

[7] Prior to the hearing, John Doe/11 stated in his affidavit that Child Doe/ 11 was a good sleeper and that her naps during the day usually lasted two to three hours. Ps' Ex. 25 ¶¶ 3-4.

Child Doe/11 was "blue in the face." Tr. at 33, 188. He "look[ed] over, and she's blue." Id. at 40. He called to his wife in the bedroom to awaken her and told her that something was wrong with Child Doe/11. Id. Jane Doe/11 came out of the bedroom to see Child Doe/11, who was face-up on the pillow on the couch. Tr. at 19. She appeared "bluish." Id. at 19-20. Child Doe/11 was not breathing, and John Doe/11 called 911 at approximately 6:49 p.m. Joint Stipulation ¶ 7; Id. at 20. John Doe/11 tried to administer cardiopulmonary resuscitation ("CPR") to Child Doe/11. Tr. at 34-35. He breathed into her mouth and applied compressions to her chest. Tr. at 41. The ambulance arrived at 6:54 p.m., within five minutes of the placed call to 911. Tr. at 21; Joint Stipulation ¶ 7
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Upon arrival at the Does' home, an emergency medical technician found Child Doe/11 lying on her back (supine) on the couch with a fire department emergency responder administering CPR. P Ex. 4 at 1. She had no heart beat or respiration. Id. She did not respond to CPR. Id. The emergency responders recorded in their patient care report Child Doe/11's "skin was warm, dry, and extremit[ies] were mottled and chest and abdomen was (sic) white . . . and [Child Doe/11's] abdomen was distended." Id.

According to the records prepared by the emergency response team, Jane Doe/11 gave the report: "[Child Doe/11] was last checked on 30 minutes [prior to ambulance arrival] and was fine. [Child Doe/11] has no medical h[istory] . . . . [C]hild did have a hep[atitis] B vaccine today." Ps' Ex. 4 at 1.

At 7:18 p.m., Child Doe/11 arrived at the emergency room where she remained unresponsive. Id. She was diagnosed as having suffered cardiopulmonary arrest of unknown cause. Ps' Ex. 5 at 6. She was pronounced dead by the emergency room doctor at 8:00 p.m. on December 21, 1994. Id. at 5.

Robert M. Anthony, M.D., a forensic pathologist in the Sacramento Coroner's office, performed an autopsy on Child Doe/11 on December 22, 1994, the day after her death. Joint Stipulation ¶ 9. He issued the Report of Autopsy on January 25, 1995. Ps' Ex. 6 at 2. Dr. Anthony recorded Child Doe 11/'s weight as 12 pounds 12 ounces and her length as 25 inches. Id. Child Doe/11's recorded weight and length differs from the recorded weight and length at her pediatric examination the day before Dr. Anthony performed her autopsy. At autospy, her weight was heavier and her length was longer.

Among the findings noted by Dr. Anthony in the section of the autopsy report under the heading of "External Description" was "a moderate amount of fixed purple livor mortis over the posterior aspects of the body surfaces." Id. at 2. The autopsy report included the weight of each of Child Doe/11's organs and a description of Dr. Anthony's findings based on his inspection of each of Child Doe/11's individual organs. See id. at

3-5. The lower extremities lacked evidence of pretibial or pedal edema. Id. at 2.

Dr. Anthony noted that Child Doe/11's bladder and stomach were both empty and that her lungs revealed "moderate pulmonary congestion and edema."[8] Id. at 4, 5. Her right lung was recorded as weighing 71 grams. Id. Her left lung was recorded as weighing 69 grams. Id. at 4.

In describing Child Doe/11's heart, Dr. Anthony noted that there were "rare epicardial petechiae," and that "[t]he epicardial surface is smooth and glistening."[9] Id. at 4. Child Doe/11's heart was recorded as weighing 28 grams. Id.

Dr. Anthony found the condition of Child Doe/11's brain to be "grossly unremarkable" with "no evidence of edema or herniation."[10] Id. at 5. Child Doe/11's brain was recorded as weighing 570 grams. Id. Dr. Anthony's inspection revealed no evidence of hemorrhage, and he noted that "[t]he meninges[11] are clear, glistening, and intact; and there is no blood in any meningeal compartment." Id.

The weights of Child Doe/11's other organs were recorded as follows:

thymus	28 grams
liver	225 grams
spleen	28 grams
right kidney	22 grams

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[8] Congestion is the "excessive or abnormal accumulation of fluid, as of blood in a part." Dorland's Illustrated Medical Dictionary 408 (30th ed. 2003). Pulmonary congestion, in particular, is the "engorgement of the pulmonary vessels." Id. Edema is "the presence of abnormally large amounts of fluid in the intercellular tissue spaces of the body, usually referring to demonstrable amounts in the subcutaneous tissues." Id. at 589.

[9] Petechiae are "pinpoint, nonraised, perfectly round, purplish red spots caused by intradermal or submucous hemorrhage." Dorland's Illustrated Medical Dictionary 1411. Epicardial is "pertaining to the epicardium or to the epicardia." Id. at 625. The epicardia is "the lower portion of the esophagus, extending from the hiatus esophagi to the cardia." Id.

[10] Herniation is the "abnormal protrusion of an organ or other body structure through a defect or natural opening in a covering, membrane, muscle or bone." Dorland's Illustrated Medical Dictionary 844.

[11] The meninges are "the three membranes that envelop the brain and spinal cord." Dorland's

left kidney 22 grams

Ps. Ex. 6 at 3-4. The autopsy report did not indicate that any of Child Doe/11's organs, other than her lungs, showed the presence of edema. See id. at 3-5. Nor did the report state whether the measured weights of Child Doe/11's organs were within the normal range for an infant of her age. Id.

In the section of the autopsy report under the heading "Pathological Diagnoses," Dr. Anthony noted the following:

> I. Well-developed, well-nourished female infant without evidence of congenital anomalies.
>
> A. Rare epicardial petechiae.

Id. at 6. Dr. Anthony recorded Child Doe/11's cause of death as Sudden Infant Death Syndrome (SIDS).[12] Id. At the time that Dr. Anthony performed the autopsy, he did not have the benefit of the detailed fact testimony of petitioners concerning the circumstances surrounding Child Doe/11's death.

II. The Opinions of the Parties' Experts

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[12] SIDS is "the sudden and unexpected death of an apparently healthy infant, typically occurring between the ages of three weeks and five months, and not explained by careful postmortem studies." Dorland's Illustrated Medical Dictionary 1833 (30th ed. 2003). Additionally, "sudden infant death syndrome" has been defined by a panel convened by the National Institute of Child Health and Human Development as "the sudden death of an infant under 1 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." Ps' Ex. 20 at 2 (Ramzi S. Cotran, et al., Robbins Pathologic Basis of Disease (6th ed. 1997) (underlined emphasis in original)(bold emphasis added)). The death usually occurs while the infant is asleep. Id. As a diagnosis of exclusion, SIDS is the rendered diagnosis when neither the autopsy, the examined death scene nor the clinical history yields an explanation for the death. See id.; see also R's Ex. FF (Marie Valdes-Dapena, M.D., Sudden Infant Death Syndrome: Pathologic Findings, Vol. 19, No. 4 Clinics in Perinatology, at 703 (Dec. 1992).

An initial diagnosis of SIDS (an unexplained sudden infant death) may be revised when additional case investigation reveals an explanation for the sudden infant death. Ps' Ex. 20 at 3. Moreover, an understanding of the cellular events and other pathological mechanisms (or pathogenesis, as defined by Dorland's at 1384) involved in a sudden infant death can be informative about the cause of the death. See id.

To address whether Child Doe/11's death resulted from her receipt of the hepatitis B vaccination administered on December 21, 1994, the parties presented experts in the areas of pathology and immunology. The experts submitted written opinions and testified before the undersigned during a recorded hearing.

Testifying for petitioners were John J. Shane, M.D., whom the undersigned accepted as an expert in the area of pathology,[13] and Alan S. Levin, M.D., J.D., whom the undersigned accepted as an expert in the area of immunology.[14]

Dr. Shane served as the Chairman of the Department of Pathology and Director of Laboratory Medicine at Lehigh Valley Hospital in Lehigh, Pennsylvania for twenty-six years. Tr. at 52-53. Stepping down from that post in August of 2000, Dr. Shane began a private consultation practice in which he continues to work full-time. Id. at 53. As a private consultant, he "performs anywhere between 30 and 60 autopsies a year." Id. Dr. Shane, by his own admission, "is not a pediatric pathologist." Id. at 56. But he has examined "hundreds" of pediatric brains on autopsy. Id. at 58.

Dr. Shane opined that Child Doe/11's "organs at autopsy were grossly unremarkable with no evidence of apparent disease process or congenital defect or anomaly. The only abnormality was a brain weight of 570 g[ra]ms and rare epicardial petechiae." Ps' Ex. 11 at 1. Dr. Shane opined that contrary to the reported findings in Child Doe/11's autopsy report, the measured brain weight of 570 grams at autopsy is evidence of cerebral edema[15] that resulted from a brain injury. See Ps' Ex. 11 at 1-2. Based on his review of Child Doe/11's medical records, which included the autopsy report and slides from the Sacramento County Coroner's Office, Dr. Shane asserted in his expert report that "the sections of [Child Doe/11's] brain are pro[of] positive of an

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[13] Pathology is "the branch of medicine that deals with the essential nature of disease, especially of the structural and functional changes in tissues and organs of the body that cause or are caused by disease." Dorland's at 1384.

[14] Immunology is "that branch of biomedical science concerned with the response of [an] organism to antigenic challenge, the recognition of self and not self, and all the biological (in vivo), serological (in vitro), and physical chemical aspects of immune phenomena." Dorland's at 914.

[15] Edema is "the presence of large amounts of fluid in the intercellular tissue spaces of the body, usually referring to demonstrable amounts in the subcutaneous tissues." Dorland's Illustrated Medical Dictionary 589.

encephalopathy." Id. at 2. Dr. Shane stated that "in the absence of other etiologic factors and with the timing of the Hepatitis B vaccination, the Hepatitis B is the obvious[,] probable and preferred etiologic mechanism for the encephalopathy which caused this child's death." Id. During the hearing, Dr. Shane testified that Child Doe/11 suffered a "respiratory death" secondary to her hepatitis B vaccination. Tr. at 89-90.

Dr. Levin also testified for petitioners. Dr. Levin is board certified in allergy and immunology and in clinical pathology. He sold his allergy-immunology practice and became a lawyer, graduating from law school in 1995. Id. at 193. He currently sees patients only on referral, and by his own testimony, sees only two or three children a year. Id. 195-197. He no longer maintains an active clinic or practice. Id. at 196. Additionally, Dr. Levin currently has a relationship with a pharmaceutical company, in which he is a seven-percent stakeholder and a board member. Id. at 193-195. Dr. Levin testified that this pharmaceutical company is a "Chinese biotech company, [which is] developing certain cytokines for treatment, . . . so [he is] very, very conversant with cytokines."[16] Tr. at 193-94.

Dr. Levin concurred with Dr. Shane that Child Doe/11's death was caused by her receipt of the hepatitis B vaccination. Dr. Levin opined in his report that Child Doe/11's vaccination led to an "excessive cytokine release followed by cerebral edema." Ps' Ex. 12 at 4. Dr. Levin explained that cytokines

> regulate the rate at which certain proteins are created or certain proteins aren't created. They control the body. . . . [C]ytokine are very, very much responsible for, among other things, inflammation, and that means that . . . when the body gets attacked by something–toxic chemical, virus or bacteria–then the body creates the reaction of inflammation.

Tr. at 199-200. According to Dr. Levin's cytokine theory, increased cytokine levels contribute to increased water content in the brain around blood vessels, a condition known as vasogenic edema. See Tr. at 203-204 (referencing Ps' Ex. 17 (an excerpt from Nelson's Textbook of Pediatrics describing cytokine-induced brain edema)). Edema in the brain results in a decreased blood flow, which can lead to death. See id.

Challenging the opinions of causation offered by petitioners' experts and testifying for respondent were Enid Gilbert-Barness, M.D., whom the undersigned accepted as an

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[16] As defined in one medical dictionary, a "cytokine" is a generic term to describe the nonantibody proteins that are released by the T-cell population, as part of a generated immune response, to the presence of an antigen. See Dorland's Illustrated Medical Dictionary 469.

expert in the field of pediatric neuropathology, and Christine McCusker, M.D., whom the undersigned accepted as an expert in the area of pediatric immunology.

Dr. Gilbert-Barness is a Professor of Pathology and Laboratory Medicine, Professor of Pediatrics, and Professor of Obstetrics and Gynecology at the University of South Florida. Id. at 113. She estimates that she has personally conducted "about 10,000" pediatric autopsies. Id. at 115. She has served on the "National Institutes of Health[] panel to examine the Sudden Infant Death Syndrome." Id. Dr. Gilbert-Barness teaches medical students on the subject of pediatric pathology. Id.

Dr. Gilbert-Barness disputed that Child Doe/11's death was related to the hepatitis B vaccination. In her opinion, Child Doe/11's death was related to an explained "Sudden Infant Death . . . [which] was very likely in this case related to an asphyxia[l] death." Tr. at 121. Dr. Gilbert-Barness opined that Child Doe/11's internal organs were congested, but she did not "think that there was a significant increase in brain weight. . . . [Nor did she] think there was significant brain edema." Id. at 122. Addressing her review of the autopsy slides, she stated that "[she] saw very little abnormality. There may have been a minimal degree of edema, but I did not see the changes that Dr. Shane has described." Id. Dr. Gilbert-Barness explained that if an encephalopathy had occurred, as Dr. Shane asserted, "one would expect to see considerable brain edema. One would also very likely – as the cause of death – see herniation of the brainstem, which was not present in this case." Id.

Dr. McCusker also testified for respondent. Certified by the Royal College of Physicians and Surgeons in Canada in general pediatrics[17] as well as in allergy and immunology, Dr. McCusker is an Assistant Professor of Pediatrics at McGill University, Associate Member of Medicine at McGill University, and a Research Director at the Meakins-Christie Laboratories of McGill. Additionally, as Director of the Clinical Immunology Lab for the Montreal Children's Hospital, Dr. McCusker has an active pediatric practice at Montreal Children's Hospital primarily in the area of allergy and immunology.

As a clinical pediatrician, Dr. McCusker disagreed with Dr. Shane's opinion that Child Doe/11's clinical presentation was indicative of an encephalopathy. Additionally, Dr. McCusker disagreed with Dr. Levin's opinion that a cytokine storm led to "an

[17] Dr. McCusker has previously been certified by the American Board of Pediatrics. Dr. McCusker stated during her testimony that she has let her American certification lapse due to the expense of maintaining several certifications. See Tr. at 239-240.

immune-mediated encephalopathy, [a] cytokine-induced encephalopathy," which, in turn, led to the death of Child Doe/11. Tr. at 243. Although Dr. McCusker agreed with Dr. Levin that cytokine activation is a normal response to vaccination, see id., she opined that the timing of Child Doe/11's death was "really too soon" to have resulted from a cytokine storm-mediated edema, id. at 258. Observing that a cytokine storm occurs as a significant reaction to an overwhelmed immune system and that a cytokine storm is distinguishable from the normal process of cytokine activation, see Tr. at 250-251, 271-272, Dr. McCusker testified that a cytokine-induced cerebral edema would have required days to manifest. Id. at 258-59.

The undersigned found the testimony of respondent's experts to be well-informed by the experts' respective professional experiences and to be well-supported by the filed medical literature. In contrast, petitioners' experts admitted the limitations of their clinical experience with pediatric populations. Additionally, the testimony regarding causation given by petitioners' experts was not supported by the facts of this particular case. On balance, the testimony of petitioners' experts was not as persuasive as the testimony of respondent's experts. Consistent with the Federal Circuit's guidance, the persuasiveness of the parties' experts must be evaluated, and the testimony of one side's experts may be rejected when a reasonable basis supports such a rejection. See Burns v. Sec'y of Dept. of Health and Human Servs., 3 F.3d 415, 417 (Fed. Cir. 1993). A decision about the persuasiveness of an expert is unreviewable on appeal. See Bradley v. Sec'y of Dept. of Health and Human Servs., 991 F.2d at 1575.

Before further addressing the opinions of the experts and examining the factual predicates for the experts' opinions, however, the undersigned reviews the applicable legal standard.

III. Discussion

A. Legal Standards

The Vaccine Injury Table lists particular injuries and conditions which, if found to have occurred within a prescribed time period, create a rebuttable presumption that an administered vaccine caused the injury or condition. 42 U.S.C. § 300aa-14(a). With respect to adverse events related to the administration of the hepatitis B vaccine, the Vaccine Injury Table lists "[a]naphylaxis or anaphylactic shock" within four hours as an "[i]llness, disability, injury or condition covered."[18] 42 C.F.R. § 100.3(a)(8)(A). The

[18] Anaphylaxis is a "a type [of] hypersensitivity reaction . . . in which exposure of a sensitized individual to a specific antigen . . . results in urticaria, pruritus, and angioedema,

Vaccine Injury Table also lists "[a]ny acute complication or sequela (including death) of an illness, disability, injury, or condition referred to above [specifically, the anaphylaxis or anaphylactic shock] which illness, disability, injury, or condition arose within the time period prescribed." 42 C.F.R. § 100.3(a)(VIII)(B).

Petitioners here have not alleged that Child Doe/11 suffered a Table injury presumptively caused by her received vaccination. Neither does the fact testimony of petitioners nor the testimony of the parties' expert witnesses appear to support such a contention. Accordingly, it is petitioners' burden to prove that Child Doe/11's death was caused by the administered hepatitis B vaccination on December 21, 1994.

As petitioners have asserted in this case, a claim for which causation is not presumed under the Act is known as an "off-Table" case. To demonstrate entitlement to compensation in an off-Table case, petitioners must demonstrate by a preponderance of the evidence that the vaccination in question caused the injury alleged. 42 U.S.C. §§ 300aa-11(c)(1)(C)(ii)(I) and (II), 300aa-13(a)(1)(A). The Federal Circuit "has interpreted the 'preponderance of the evidence' standard referred to in the Vaccine Act as one of proof by a simple preponderance, of 'more probable than not' causation." Althen v. Sec'y of Dept. of Health and Human Servs., 418 F.3d 1274, 1279 (Fed. Cir. 2005) (citing Hellebrand v. Sec'y of Dept. of Health & Human Servs., 999 F.2d 1565, 1572-73 (Fed. Cir.1993)). Proof of medical certainty is not required. See Bunting v. Sec'y of Dept. of Health and Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991).

Petitioners satisfy their burden of proving causation by demonstrating: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between the vaccination and injury." Althen, 418 F.3d at 1278.

B. Evaluating the Presented Evidence

Consistent with the remand order, the undersigned addresses explicitly and separately whether petitioners have satisfied each of the prongs of the Althen standard.

1. A medical theory causally connecting the vaccination and the injury

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followed by vascular collapse and shock and [is] often accompanied by life-threatening respiratory distress." Dorland's Illustrated Medical Dictionary 73.

To prove causation, petitioners first must offer a medical theory causally connecting Child Doe/11's receipt of her hepatitis B vaccination and her death.[19] Althen, 418 F.3d at 1278. Through their experts, Dr. Shane and Dr. Levin, petitioners advanced a theory of vaccine causation. Dr. Shane, petitioners' expert in pathology, opined that Child Doe/11's death was the result of an acute encephalopathy[20] caused by her receipt of the hepatitis B vaccination. Ps' Ex. 11 at 1-2; Tr. at 88. In his written report, Dr. Shane stated "that this case represents an encephalopathic death with unequivocal microscopic findings of an encephalopathy; [and] microscopic central nervous system findings that are inconsistent with a SIDS death." Ps' Ex. 11 at 2. His opinion rested heavily on his view that Child Doe/11's measured brain weight of 570 grams at autopsy was a "heavy" brain and was indicative of "moderate to moderately severe cerebral edema" that resulted from a brain injury that Child Doe/11 had suffered prior to her death. Tr. at 68-69; see also Ps' Ex. 11 at 1-2 (Dr. Shane's report).

Petitioners' expert, Dr. Levin, opined that the administration of Child Doe/11's hepatitis B vaccination produced an excessive release of cytokines, which caused, in turn, brain edema, encephalopathy and death. Ps' Ex. 12 at 4 (Dr. Levin's report); Tr. at 201-215. Describing hepatitis B as a "superantigen," Dr. Levin explained that in Child Doe/11's situation, the release of two particular cytokines (IL-1 and TNG) was "provoked by the hepatitis B," and the release of those cytokines began to have a cytotoxic effect on the lining of Child Doe/11's blood vessels that led to swelling in the surrounding tissues and the acute encephalopathy that Child Doe/11 suffered. See Tr. at 207-209, 214.

In satisfaction of the first prong of Althen, petitioners have offered a medical theory causally connecting Child Doe/11's vaccination and her injury.

2. A logical sequence of cause and effect showing that the vaccination was

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[19] While the law does not require absolute precision in identifying the medical mechanism of injury, there must be "sufficiently compelling proof that the agent must have caused the damage somehow." Kennedy v. Collagen Corporation, 161 F.3d 1226, 1230 (9th Cir. 1998) (quoting Daubert v. Merrell Dow Pharmaceuticals. Inc., 43 F.3d 1311, 1314 (9th Cir.), cert. denied, 516 U.S. 869 (1995)).

[20] An acute encephalopathy is a defined as "any degenerative disease of the brain" that has a short and relatively severe course. Dorland's Illustrated Medial Dictionary 25 (defining acute), 610 (defining encephalopathy). The condition is also defined as "any disorder of the brain" having a rapid onset and a severe health effect. Stedman's Medical Dictionary (28th ed. 2006) 23 (defining acute), 636 (defining encephalopathy).

the reason for the injury

As the Federal Circuit has observed, petitioners' offered medical theory is persuasive when accompanied by "'proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury[,]' the logical sequence being supported by 'reputable medical or scientific explanation [,]' i.e., 'evidence in the form of scientific studies or expert medical testimony[.]'" Althen, 418 F.3d at 1278 (quoting Grant, 956 F.2d at 1148)).

The sequence of vaccine-related cause and effect that petitioners have advanced is not supported by the facts of this case. The undersigned first addresses petitioners' claim that Child Doe/11 suffered an encephalopathy as a result of receiving the hepatitis B vaccination. The undersigned then addresses petitioners' claim that Child Doe/11's injury resulted from a vaccine-induced cytokine storm.

a. Examining whether Child Doe/11's clinical and pathological presentation supports a finding that she suffered an encephalopathy

i. The opinion of petitioners' pathologist

As expressed in his written report, petitioners' pathologist, Dr. Shane, found that Child Doe/11's "organs at autopsy were grossly unremarkable with no evidence of apparent disease process or congenital defect or anomaly." Ps' Ex. 11 at 1. He noted that "[t]he only abnormality was a brain weight of 570 g[ra]ms and rare epicardial petechiae." Id. Dr. Shane pointed to the measured brain weight of 570 grams as evidence of an "increased brain weight." Id. He explained that the increased brain weight together with the "clear spaces" around the blood vessels of the brain that he observed during his review of the autopsy slides are evidence of cerebral edema and an encephalopathy that led to Child Doe/11's death. Id. at 1-2. He explained:

> [H]alos or clear spaces surrounding the blood vessels . . . [in] the brain . . . is the microscopic give-away of cerebral edema. You can approximate the severity of that cerebral edema by the extent of the spaces. It is a subjective call on the basis of the examiner. It becomes a little bit more precise –[but] still subjective [when] you tie into your assessment . . . the gross weight of the brain."

Tr. at 59-60. Based on the microscopically observed "halo" formation around the blood vessels (also described as perivascular spaces) in Child Doe/11's brain, Dr. Shane expressed the "subjective" view that Child Doe/11's brain was "moderate[ly] to very

prominent[ly]" edematous. Id. at 63.

Dr. Shane added that he microscopically observed "early neuronal necrosis" in Child Doe/11's brain. Ps' Ex. 11 at 1. He explained during the hearing that "when the brain swells, . . . it becomes edematous, the oxygen supply to the brain, to the[] neurons is diminished, and they will begin to undergo degenerative change, and it's those changes that I found in these neurons in this particular brain." Id. at 61. He attributed the "hypoxic change" (or reduced oxygen flow) in Child Doe/11's neurons to her brain edema. Id. Dr. Shane testified that "it takes a matter of hours for neuronal degeneration to appear . . . even [with] mild hypoxia." Id. at 61-62.

Expanding upon his written opinion during the hearing, Dr. Shane asserted that Child Doe/11 "had heavy organ syndrome." Tr. at 103. Dr. Shane asserted that "the liver, the lungs, the spleen–even the kidneys are heavy, and yet I do not see significant patho-congestive change [or evidence that Child Doe/11's organs were engorged with blood], so I must relate the heavy organs to edema." Id.

Dr. Shane opined that "in the absence of other etiologic factors and with the timing of the Hepatitis B vaccination, the Hepatitis B is the obvious[,] most probable and preferred etiologic mechanism" for Child Doe/11's encephalopathic death. Ps' Ex. 11 at 2. During the hearing, Dr. Shane described how the encephalopathy caused Child Doe/11's death. Tr. at 88-91.

He explained that vasogenic edema occurs when the epithelial lining of the blood vessels "separate" and permit fluid to penetrate through the "disrupted" lining of the blood vessels into the tissues. Id. at 89. "[A]s that accumulates, it fosters an atmosphere in th[]e brain[] . . of hypoxia.[21] It also fosters in th[e] brain less receptivity to the stimulus of carbon dioxide, and these children in truth die a respiratory death, that is a death of respiratory cessation or respiratory failure, and that's the manner of death." Id. (footnote added). Dr. Shane stated during his testimony that with "encephalopathies, the edema comes first, then the hypoxia follows." Id. at 90. He added that hypoxia can contribute to an edematous condition. See id.

In addition to the pathological findings that informed Dr. Shane's opinion, he reasoned that "in the presence of a clinical scenario of a recent vaccination followed by the expected signs and symptoms clinically of an encephalopathy, namely weakness,

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[21] Hypoxia is the "reduction of oxygen supply to tissue below physiological levels despite adequate perfusion of the tissue by blood." Dorland's 900.

somnolence, and a reduced level of consciousness," this is a case of "an encephalopathic death." Ps' Ex. 11 at 2.

In discussing the clinical symptoms of an encephalopthy in a recently vaccinated child, Dr. Shane conceded that he is "not a clinical pediatrician," that he is "not a good resource for how kids react to vaccinations," and that clinical pediatrics is "not an area where [he is] expert." Tr. at 87. He stated that how a child might be expected to react to a routine vaccination is a question "best ask[ed] . . . [of] a person who does clinical pediatrics, and sees large numbers of these children post vaccination." Id. He further stated that he "would defer . . . to . . . a pediatrician who sees children every day and gives them vaccinations." Id. Nonetheless, he expressed the view, based on his self-described "limited knowledge," that "it's abnormal" for a two-month old to be lethargic and not hungry following a routine vaccination. Id.

With respect to the particular link between a hepatitis B vaccination, a systemic cytokine release, and an encephalopathy, Dr. Shane stated that he would defer to the immunologists to interpret the literature. Id. at 98. He observed that "there is [medical] literature on both sides" of the issue of whether a received hepatitis B vaccination leads to an acute encephalopathy in young infants. Id. at 98-99.

ii. Opinion of Respondent's Experts

Respondent's expert in neuropathology, Dr. Gilbert-Barness, testified that the expected signs and symptoms of an encephalopathy would include seizures, vomiting, high-pitched screaming, and in the presence of brain herniation, marked somnolence. Id. at 136-138. Dr. Gilbert-Barness explained that one would see "not only somnolence but coma, because if this brain had herniated . . . there would have been coma." Id. at 37. Brainstem herniation triggers a cardiorespiratory response that leads to death. Id. at 137-138. Child Doe/11 did not have seizures, did not vomit, and did not emit high-pitched screams during the hours following her vaccination and prior to her death. Although Child Doe/11 was described as sleepy following her vaccination, Dr. Gilbert-Barness distinguished the sleepiness that ordinarily follows a vaccination from the somnolence associated with an encephalopathic condition. See id. at 139. Dr. Gilbert-Barness testified that a period of "up to 12 hours "would be required to "have severe enough symptoms to cause death." Id.

Respondent's second expert, Dr. McCusker, who is board certified in general pediatrics and in immunology, testified that most pediatricians would not view a "sleeping" child who has received a vaccination as "outside of keeping with the norms." Tr. at 262. Based on her emergency room examination of "10 or 15 children who were

encephalopathic," she explained that the type of severe somnolence that is indicative of an encephalopathy is distinguishable from the type of somnolence that pediatricians fully expect to follow a vaccination. See id. In describing the clinical presentation of a child who has suffered an acute encephalopathy, Dr. McCusker explained that "[i]t's a child who's very, very sleepy, difficult to rouse – usually impossible to rouse. . . . [S]o you look at whether or not they respond to voice, whether or not they respond to minor stimulus or major stimulus, [whether] they respond to pain." Id. "If they don't respond to pain but they're still alive, that's severe somnolence." Id.

Dr. McCusker continued that "usually–the somnolent component is the end. The beginning is an agitated, irritated child." Id. at 263. Parents report that the child has been cranky "for two or three days," the child has "had some fever," and the child has been vomiting. Id. The child will begin to refuse food and the vomiting may nonetheless continue because of the increased intracranial pressure. Id. at 263-264. Seizures occur and somnolence follows. Id. at 264. It is usually the onset of seizures that prompts the family to seek emergent medical attention. See id.

The testimony of respondents' experts regarding the common symptoms of an encephalopathy and the degree of unresponsiveness observed in an encephalopathic child is supported by the Vaccine Act's definition of an encephalopathy in association with a Table Injury. Although not dispositive in this case because this case does not involve a Table Injury, the Act's definition of an encephalopathy in association with a Table Injury is instructive on the issue of what types of symptoms would support a finding, for Vaccine Act purposes, that an encephalopathy has occurred.

Under the Vaccine Act, an encephalopathy is a listed injury on the vaccine Injury Table, and if an encephalopathic condition manifests within three days after the administration of particular vaccines (which do not include the hepatitis B vaccination), vaccine causation is presumed for the encephalopathic condition. See 42 U.S.C. § 300aa-14(a). The Vaccine Act defines an encephalopathy to mean "any significant acquired abnormality of, or injury to, or impairment of function of the brain." 42 U.S.C. § 300aa-14(b)(3)(A) (Supp. 2002). The Vaccine Act provides:

> Among the frequent manifestations of encephalopathy are focal and diffuse neurologic signs, increased intracranial pressure, or changes lasting at least 6 hours in level of consciousness with or without convulsions. The neurological signs and symptoms of encephalopathy may be temporary with complete recovery, or may result in various degrees of permanent impairment. Signs and symptoms such as high pitched and unusual screaming, persistent unconsolable crying, and bulging fontanel are

compatible with an encephalopathy, but in and of themselves are not conclusive evidence of encephalopathy. Encephalopathy can usually be documented by slow wave activity on an electroenephalogram.

Id. The regulatory qualifications and aids to interpretation of the Vaccine Injury Table, which are set forth at 42 C.F.R. §100.3(b)(2)(i), describe an acute encephalopathy as one that is sufficiently severe that, whether or not hospitalization occurs, the condition requires hospitalization. 42 C.F.R. §100.3(b)(2)(i).

The vaccine regulations further provide that 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. Id. For those children less than 18 months of age who present following a seizure, the children shall be viewed as having suffered an acute encephalopathy if their significantly decreased level of consciousness persists beyond 24 hours and cannot be attributed to a seizure or medication. Id.

The symptoms described in the Vaccine Act and in the regulations that are indicative of an encephalopathy are consistent with the symptoms that respondent's experts described.

iii. The clinical presentation of Child Doe/11

Petitioners testified during the hearing that Child Doe/11 was lethargic and fell asleep after she received her vaccination and that she refused to eat.[22] Dr. Shane expressed the opinion that Child Doe/11's lethargy and disinterest in eating was an "abnormal" reaction to the administration of a vaccination. Although he stated that Child Doe/11's clinical presentation after her vaccination was consistent with the "expected signs and symptoms . . . of an encephalopathy[,] namely weakness, somnolence, and a reduced level of responsiveness," Ps' Ex. 11 at 2, Dr. Shane acknowledged that on the question of whether a vaccinated child would be expected to be somnolent, he "would defer . . . to a pediatrician who sees children every day and gives them vaccinations." Tr. at 87. As he stated during the hearing, he would defer to the expertise of a pediatrician because he is not a clinical pediatrician and his knowledge on the subject is "limited." Id.

Absent from Child Doe/11's medical records are any references to symptoms of

[22] Among the emergency room records documenting the continued efforts to resuscitate Child Doe/11 after her arrival at the hospital is a notation that her diaper had stool in it. Ps' Ex. 5 at 3.

irritability, fever, vomiting, or seizures after her vaccination. The symptoms that Child Doe/11's parents described during the hearing were her sleepiness and her refusal to eat. Additionally, the testimony of Child Doe/11's mother suggested that although Child Doe/11 was tired after her vaccination, she did awaken during the time that the family shopped after Child Doe/11's pediatric visit.

Moreover, although petitioners' expert, Dr. Shane, described Child Doe/11's symptoms after her vaccination as abnormal, he expressed a willingness to defer to the opinion of a pediatrician on the issue of whether sleepiness and refusal to eat is a normal reaction to a received vaccination. Here, Dr. McCusker, a board-certified pediatrician with an active clinical practice, testified that Child Doe/11's sleepiness and lack of appetite was a normal reaction to her vaccination and that she never had any of the clinically recognized symptoms that precede the severe somnolence that is indicative of an encephalopathy. That Child Doe/11's parents are lay persons, not medical personnel, and as they asserted in their post-hearing reply brief, "simply did not know any better," see Petitioners' Post-Hearing Reply Brief at 14, does not make it more likely than not that the described sleepiness and lack of appetite in Child Doe/11 after her vaccination was tantamount to the "significantly decreased level of consciousness" that is indicative of an encephalopathy. The described symptoms in Child Doe/11 fall within the range of a normal response to a vaccination, and Child Doe/11's father asserted that she was a good napper, ordinarily taking naps of 2-3 hours. See Ps' Ex. 25 at ¶ 4. Informed by the medical records and the testimony of the parties' experts, the undersigned is not persuaded, in the absence of other evidence that would support a finding that Child Doe/11 suffered an encephalopathic injury, that Child Doe/11's described somnolence was indicative of an occurring encephalopathy.

iv. The pathological findings from Child Doe/11's autopsy

A. Child Doe/11's brain

As recorded in the autopsy report, Child Doe/11's brain weighed 570 grams. Ps' Ex. 6 at 5. She was seven weeks and a couple of days old (nearly two months old) at the time of her death. See Ps' Ex. 2 at 2; Ps' Ex. 5 at 6. In discussing and evaluating the significance of Child Doe/11's measured brain weight, petitioners' pathologist, Dr. Shane, referred to the table of weights of organs of female infants contained in the tenth edition of Anderson's Pathology, a standard medical school textbook. See Tr. at 64 (referencing Ps' Ex. 19 at 2 (Anderson's Pathology (Ivan Damjanov, M.D., Ph.D. & James Linder, M.D. eds., 10th ed. 1996)). The listed mean (or average) brain weight for a female infant

of two months of age is 490 grams.[23] Ps' Ex. 19 at 2. The listed standard deviation for the brain weight of a two-month old is 51 grams. Id. As Dr. Shane explained during his testimony, the standard deviation provides "a range" within which the weight of the brain or other measured organ is expected to fall for a "particular age group" of children. Tr. at 68. Rounding the standard deviation from 51 to 50, Dr. Shane identified the expected range for the brain weight of a two-month old female to be "440 [grams] to 540 [grams]." Tr. at 69. Because Child Doe/11's brain was 30 grams heavier than "the absolutely heaviest one we'd expect," Dr. Shane described the brain weight as increased. Id. Putting the "increased" brain weight "together with what we see microscopically," Dr. Shane opined that "this child has moderate to moderately severe cerebral edema." Id. Dr. Shane testified that "[w]ithout cerebral edema, without the brain weight, [he] would certainly have very little on which to base a diagnosis of an encephalopathic death." Tr. at 98.

Dr. Shane acknowledged during his testimony that the evaluation of edema is a "subjective call on the basis of the examiner." Id. at 60; accord R's Ex. LL at 10 (noting that "the evaluation of oedema is difficult, subjective, and particularly uncertain in brains from new-born infants"). According to Dorland's Medical Dictionary, a newborn infant is defined as "human young during the first four weeks after birth." Dorland's at 927. Although Child Doe/11 was not, by this definition, a newborn, the undersigned appreciates that the evaluation of the degree of edema at autopsy is determined by microscopic observation of the brain and involves a subjective assessment of the amount of the observed clear spaces that are described as indicative of mild, moderate, or severe edema.

In response to questioning from the undersigned, Dr. Shane also addressed the significance of the listed standard error of 14 grams under the brain weight of 490 grams in the referenced textbook. Tr. at 105. Dr. Shane agreed that a standard error of 14 grams would mean that the mean brain weight could fall either 14 grams above or 14 grams below the mean brain weight of 490 grams. Id. Dr. Shane explained that generally standard error is introduced by unremoved "exogenous material" such as "unremoved cerebral spinal fluid [or] pieces of attached dura . . . that would not be considered part of the brain weight." Id. at 105-106. Adjusting the mean brain weight to include both the standard error and standard deviation and to reflect the upper limit of the brain weight, 555 grams would be the "top limit of normal."[24] Id. at 106.

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[23] See Dorland's 1108 (defining mean).

[24] The brain weight calculation in the transcript reflects a mathematical error.

Respondent's pathologist, Dr. Gilbert-Barness, disagreed with Dr. Shane's impression of Child Doe/11's brain weight. In her view, there was neither a "significant increase in brain weight" nor was there "significant brain edema." Tr. at 122. In support of her opinion, she relied on different brain weight charts than did Dr. Shane. See Respondent's Ex. EE at 3-4 (Handbook of Pediatric Autopsy Pathology, Ch. 2, App. 29 and App. 37 (2005)). While noting that she had written a chapter in the Anderson textbook, Dr. Gilbert-Barness testified that she "[did not] know of any pediatric pathologists who . . . use that table." Tr. at 131 (emphasis added). Commenting that she had "some data that is quite up to date" in her new edition of a pediatric pathology textbook, she stated that the current organ weight data for children is "very close to . . . the [data in] Appendix 37 from the Handbook of Pediatric Autopsy Pathology," the resource on which she relied to assess Child Doe/11's brain weight.[25] Id.

At Appendix 37, in the Handbook of Pediatric Autopsy Pathology textbook is a table entitled, "Brain Weight as a Function of Age in Children and Adolescents." R's Ex. EE at 4. The listed median brain weight for a two-month old girl in that table is 560 grams, which is 10 grams lighter than Child Doe/11's brain weighed at autopsy.[26] See id.; Ps' Ex. 6 at 5. From that same textbook, Handbook of Pediatric Autopsy Pathology, respondent also filed Appendix 29, entitled "Organ Weights in Children." R's Ex. EE at 3. In that table, the listed median brain weight for a seven to nine week old is 489 grams. Id. In that same table, the listed median brain weight for a two to three month old is 516 grams. Id. The standard deviations for the listed brain weights in the tables provided by respondent were unknown. Tr. at 130.

The listed median brain weight for a two-month old in the tables of organ weights

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[25] In response to questioning from the undersigned, Dr. Gilbert-Barness explained that the organ weight tables for children are periodically updated. Tr. at 131.

[26] This table is compared to other brain weight surveys of children in Respondent's Exhibit LL at 5. (J. Voigt and H. Pakkenberg, Brain Weight of Danish Children, Acta Anat. 166:290-301 (1983)). In addressing the comparison of the results of the authors' study and the various previously published brain weight surveys, the authors noted that "our results are systematically higher as far as all age groups are concerned. This may result from the fact that . . . only healthy children or children with illnesses of short duration are included in our material." Rs' Ex. LL at 11. The authors "emphasized that most of the cases [involved in the previously published studies] are hospital patients, i.e. sick children, which can influence the brain weight." Id. at 6. "[I]n the . . . hospital series [cases] previously examined[,] the majority of the data in all probability was derived from children suffering from prolonged illnesses. Id. at 10.

provided by the parties for the undersigned's consideration are variously 489 grams, 490 grams, 516 grams and 560 grams. According to petitioner's own expert, a brain weight of 540 grams (if the median weight is adjusted upward by the listed standard deviation) or 555 grams (if the median brain weight is adjusted upward for both the listed standard error and the listed standard deviation) represents the high end of the normal range of a two-month old's brain weight. Although the standard deviation is not known for the median brain weight of 560 grams for a two-month-old girl, as listed in one of the tables provided by respondent, Child Doe/11's measured brain weight of 570 grams is ten (10) to thirty (30) grams heavier than the top range of normal brain weights or the highest listed median brain weight in any of the tables provided to the undersigned. Based on the provided tables of brain weights, Child Doe/11's measured brain weight at autopsy reflected a marginally increased brain weight beyond the heaviest listed brain weights that would be considered to be within the normal range for her age group.

The parties' experts were questioned about whether there was any correlation between the heavier organ weights and heavier body weights because Child Doe/11's body weight was in the ninetieth percentile both at birth and at her two-month pediatric examination when she received the vaccination at issue in this proceeding. Additionally, Child Doe/11's head circumference as measured at the two-month examination was in the ninetieth percentile. The parties' experts had differing views on the correlation between body weight and the weight of a child's organs. Dr. Shane testified that Child Doe/11, who is documented in her growth charts as an eleven pound baby (in ninetieth percentile for weight) of "normal--or average height or length" (in the fiftieth percentile for length), "is not an exceedingly large baby." Tr. at 162. Dr. Shane explained that even in cases involving obese persons, "obesity doesn't increase the weight of your organs." Id.

Dr. Gilbert-Barness testified that Child Doe/11's weight of eleven pounds at seven weeks of age, while within normal limits, was on the heavier side and that body weight corresponded to "somewhat heavier than normal" organs. Id. at 133-134. Dr. Gilbert-Barness stated that based on Child Doe/11's recorded weight, her "organs would be expected to be on the high side of the normal." Id. at 136.

Studies indicate that brain weight is dependent on age during childhood. Rs' Ex. LL at 10. Brain weight is also dependent on height, and "there is a close correlation between body height and age." Id. At least one study has indicated that brain weight increases after death, "mostly during the first 12 h[ours] after death, then more slowly, totalling an average of about 9%." Id. Because autopsies "are always carried out considerably later than 12 h[ours] after death, the measured brain weight at autopsy should be approximately 9% above the the brain weight in vivo. Id. In this case, Child Doe/ 11 was pronounced dead by the emergency room doctor at 8:00 p.m. on December

21, 1994. Ps' Ex. 5 at 6. Her autopsy was performed the next day, on December 22, 1994 at 8:40 a.m., more than twelve hours after her death. Ps' Ex. 6 at 2.

Of important note in evaluating Child Doe/11's brain weight is the inconsistent recordings of Child Doe/11's length, both at birth, at her two-month pediatric examination, on her growth charts, and on the autopsy report.[27] Compare Ps' Ex. 3 at 7 (undated pediatric growth chart reflecting a body length at birth of roughly twenty and one-fourth inches (or 51.5 cms)) with Ps' Ex. 3 at 1, 3 (recording a body length of 21.75 inches (or 55 cms) on October 31, 1994, Child Doe/11's date of birth) with Ps' Ex. 3 at 1 (recording a body length of twenty and one-fourth inches on November 9, 1994, nine days after Child Doe/ 11's birth) with Ps' Ex. 3 at 3 (recording a body length of twenty-one and three-fourths inches on December 21, 1994, the date of Child Doe/11's two-month pediatric examination and the date of her death) with Ps' Ex. 3 at 7 (undated pediatric growth chart reflecting a body length at her two-month pediatric examination of roughly twenty-one and one-half inches (or nearly 55 cms)) with Ps' 6 at 1, 2 (reporting a body length of twenty-five inches in the Coroner's Report and the Report of Autopsy). The differences in the recorded body length undoubtedly reflect the difficulty in measuring the length of a baby who may be squirming or have her legs curled.

Child Doe/11's approximate body length prior to her death is an important determination in this case because it affects the percentile into which Child Doe/11 fell for body length and a child's body length is a variable that correlates to a child's brain weight. The correlation between body length and brain weight informs the undersigned's evaluation of whether Child Doe/11's pathological presentation at autopsy, particularly her brain weight, was as abnormal as petitioners have asserted.

Notably, the initial hospital body length measurement of 21.75 inches (or 55 cms) placed Child Doe/11 in the ninety-fifth percentile for length.[28] If true, Child Doe/11's body length would not be average, as described by Dr. Shane, but would correspond to an above-average baby, nearly at the top of the length chart. The body length measurement on which Dr. Shane relied was contained in Child Doe/11's pediatric records and was derived from her pediatric growth chart. The undersigned, however, credits the measurement recorded in the hospital records on the date of Child Doe/11's birth as the

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[27] In contrast, the reported body weights at birth and at Child Doe/11's two-month pediatric examination are consistent.

[28] This percentile is determined by reference to the pediatric growth chart filed as Ps' Ex. 3 at 7.

most contemporaneous measurement of Child Doe/11's body length at birth and an indication of her earliest recorded length, which exceeded average length. Using the growth differential reflected on Child Doe/11's pediatric growth chart of roughly one and one-fourth inches, the undersigned finds that Child Doe/11's body length as measured at her two-month pediatric examination was nearly twenty-three inches (or 58.5 cms) which places Child Doe/11 in the ninety-fifth percentile for body length. The undersigned observes that this body length is still two inches shorter than Dr. Anthony measured at autopsy, which is the longest recorded body length for Child Doe/11 reported in the filed records. The undersigned takes note of the body length recorded in the autopsy report as additional evidence that the majority of the recorded measurements of Child Doe/11's body length militate in favor of a finding that she exceeded average length. The undersigned further notes that the difficulties associated with measuring the length of a squirming baby were not present at the time that Dr. Anthony recorded his measurements.[29]

The factual record militates in favor of a finding that Child Doe/11 was a long baby. Based on Dr. Shane's own testimony correlating body length and brain weight, Child Doe/11's brain weight cannot be viewed, as Dr. Shane has urged, from the perspective that Child Doe/11's big brain was disproportionate to her average length.

Moreover, respondent's expert, Dr. Gilbert-Barness, testified that based on her review of the autopsy slides, she "saw very little abnormality." Tr. at 122. She allowed that "[t]here may have been a very minimal degree of edema" but she did "not see the changes that Dr. Shane described." Id. Dr. Gilbert-Barness disagreed with Dr. Shane that the microscopic observations of Child Doe/11's brain supported a finding that an encephalopathy had occurred. She explained that, "if it were an encephalopathy, one would expect to see considerable brain edema. One would also very likely–as the cause of death–see herniation of the brainstem, which was not present in this case, and some of the changes that [Dr. Shane] has described . . . . But I did not observe that." Tr. at 122-123. Moreover, she noted the "absence of clinical evidence" that an encephalopathy had occurred. Id. at 137.

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[29] There is a strong argument to be made that the measurement of Child Doe/11's length at autopsy is the proper measurement of length for the undersigned to consider in this case because that measurement was not complicated by the difficulties associated with measuring the length of a squirming baby and because the measurement of her length at autopsy is the measurement of interest for correlation to her measured brain weight at autopsy. It is sufficient for the purpose of this decision, however, that the preponderance of the evidence in this case indicates that Child Doe/11 was well above average length for her age.

Having considered the experts' testimony and filings pertaining to brain weights for children of particular ages, the evidence of Child Doe/11's brain weight and body length, the experts' testimony pertaining to the amount of clear space seen in Child Doe/11's brain, and the experts' testimony regarding the clinical symptoms of an encephalopathy in this case, the undersigned is not persuaded that Child Doe/11's brain weight, as determined at autopsy, was as abnormally heavy as Dr. Shane suggested and reflected the significantly edematous condition that Dr. Shane claimed. Rather, it is the view of the undersigned that Child Doe/11's brain as measured at autopsy was not out of proportion with her body length and weight and not much beyond, if at all beyond, the range of normal brain weight for an infant of Child Doe/11's age according to the tables included in the pathology textbook excerpts filed in this case. Moreover, having put Child Doe/11's brain weight into proper perspective, it is the view of the undersigned that Child Doe/11's brain, as observed microscopically, did not reflect as severe an edematous condition as described by Dr. Shane, who relied in part on Child Doe/11's brain weight to inform his interpretation of the autopsy slides.

B. Child Doe/11's Other Organs

Dr. Shane also addressed the weight of Child Doe/11's other measured organs and asserted during the hearing that Child Doe/11 had "heavy organ syndrome." Tr. at 103. Indeed, the parties' respective pathologists and the pathologist who performed Child Doe/11's autopsy unequivocally agreed that the weight of Child Doe/11's lungs was abnormal. See Tr. at 108 (Dr. Shane describing as "heavy"), 124 (Dr. Gilbert-Barness describing as "considerably greater than . . . the normal"); Ps' Ex. 6 at 4 (Dr. Anthony described "moderate pulmonary congestion and edema"). As recorded in the autopsy report, Child Doe/11's right lung weighed 71 grams and the left lung weighed 69 grams. Ps' Ex. 6 at 4. The weight for lungs combined is listed as 74 grams (with a 23 gram standard deviation) in the organ weight table supplied by petitioners from Anderson's Pathology textbook. Ps' Ex. 19 at 2. The weights for the respective lungs listed in the table of organ weights contained in the Handbook of Pediatric Autopsy Pathology textbook are 32 grams for the right lung and 29 grams for the left lung for a seven to nine-week old. See R's Ex. EE at 3. Although the standard deviation was unknown for the weights listed in the table from the Handbook of Pediatric Autopsy Pathology textbook excerpt filed by respondent, the weight of the Child Doe/11's lungs (which, depending upon the table to which one refers, was nearly thirty to fifty percent heavier than the weight listed for lungs in the filed weight tables), and the microscopic appearance of the lungs appears to have impressed similarly both the parties' pathologists and the pathologist who conducted the autopsy as an abnormal finding.

Child Doe/11's liver and spleen were also heavier than the listed table weights for

those respective organs. See Ps' Ex. 6 at 4-5 (autopsy report); Ps' Ex. 19 at 2 (organ weight table from the Anderson's Pathology textbook); R's Ex. EE at 3-4 (tables of organ weights from the Handbook of Pediatric Autopsy Pathology textbook). However, Dr. Shane testified that under the microscope he could not see edema in either her liver or her spleen even though he could see edema in her brain. Id. at 103-104. He reasoned that because the child had "heavy organs," her "heavy organs must be explained on the basis of edema." Id. at 104 (emphasis added). He opined that "[t]he edema would certainly be consistent with a systemic cytokine relationship." Id.

In the absence of clinical symptoms of an encephalopathy, Dr. Gilbert-Barness expressed the view that Child Doe/11's heavy organ weights are consistent with and could be explained by an asphyxial death, a manner of death which could explain a previously unexplained SIDS death. See Tr. at 137, 141. She explained that a child's organs become heavy when a child is asphyxiated because the cutting off of the child's airway causes hypoxia; the blood vessels become dilated and the organs become congested with blood. Id. at 142. As noted in her written report, Dr. Gilbert-Barness saw congestion in the slides of Child Doe/11's organs. Tr. at 144-145 (describing, on microscopic examination, "marked congestion of the viscera, particularly the spleen, kidneys and adrenal glands"). She also noted some congestion in the lungs and in the liver, findings which were reflected in the autopsy report as well. See Tr. at 145-146 (explaining that a congested liver would appear dark red brown in color while an uncongested liver would have a light brown coloring); Ps' Ex. 6 at 4 (autopsy report describing congestion and edema in the lungs and the dark-red brown coloring of the liver). Based on her review of the case, Dr. Gilbert-Barness opined that Child Doe/11's death was not an unexplained SIDS death, but rather a sudden infant death which was explained by accidental asphyxiation. Tr. at 151.

Dr. Shane disagreed with Dr. Gilbert-Barness's opinion regarding the likelihood of a SIDS death. In his submitted written report, Dr. Shane stated that Child Doe/11's death was not a Sudden Infant Death Syndrome death, as reflected in the autopsy report, because there was no evidence of an antecedent respiratory illness or a medical history of "respiratory difficulties" and there were no abnormal pulmonary findings. Ps' Ex. 11 at 2. Moreover, Dr. Shane stated that the observed "epicardial petechial hemorrhage" on autopsy was "the result of and consistent with the resuscitative attempts." Id. at 1. Dr. Shane's description of Child Doe/11's lungs as "heavy," see Tr. at 108, but not "abnormal," see Ps' Ex. 11 at 2, was contradictory and was inconsistent with his expressed view about the significance of Child Doe/11's "heavy" organs. Dr. Shane attributed the weight of the organs to the presence of edema.

Dr. Shane did agree with Dr. Gilbert-Barness that an increase in organ weight

could occur as a result of congested blood vessels in the organs, and he explained that in the circumstance of significantly increased organ weight, edema occurs in the extremities in addition to the congestion.[30] Tr. at 164. The autopsy report, however, expressly noted the absence of evidence of edema in the lower extremities, see Ps' Ex. 6 at 2, and Dr. Shane testified that he did not see the congestive changes that would account for the organ weights measured in Child Doe/11. Tr. at 165. Dr. Shane also acknowledged during his testimony that he did not see edema either in Child Doe/11's liver or spleen. See Tr. at 103-104. He opined, nonetheless, that attributing the weight of Child Doe/11's organs to edema would be consistent with petitioners' theory of a cytokine-induced encephalopathy. Id. at 104.

In evaluating the significance of Child Doe/11's other organ weights, both parties' experts addressed the characteristic pathological findings in SIDS deaths that are explained by a respiratory failure of some type. The experts' discussion and the context of the discussion merits mention here.

I. Characteristic pathological findings in SIDS deaths that are explained

In an effort to show that there were no other possible causes for Child Doe/11's death, other than the hepatitis B vaccination that she had received, Dr. Shane made an effort to eliminate SIDS as a possible cause of death in his filed expert report. See Ps' Ex. 11at 2. Dr. Shane opined in his report that the circumstances surrounding Child Doe/11's death and the pathological findings at Child Doe/11's autopsy were "inconsistent with a SIDS death." Id.

During the hearing, Dr. Shane testified that when addressing SIDS as a cause of death, a "historical perspective" is appropriate. Tr. at 77. He explained that the syndrome began as an "Unexplained Infant Death Syndrome, and the body of science – which continues to evolve– . . . has evolved in the last decade . . . so that the unexpected aspect of Sudden Infant Death Syndrome has disappeared, and . . . it [has] become a definable disease process." Tr. at 77-78. He further explained:

> As part of the "definable disease process, there are [particular] findings. These children frequently have upper respiratory problems before their sudden demise. And in terms of the pathologic findings, [there are] a number of multi-organ findings that we see in these cases. Not all cases

[30] Dr. Shane explained that congestion reflects the heart's failure to adequately distribute blood throughout the body and such congestion can occur in cases of heart failure. Tr. at 163-164.

> will have all of the findings, but most of the cases should have at least some of the findings, and some of the findings, of course, include some of these children can have cerebral edema if . . . the death occurred over a period of time, they can have some secondary edema."

Id. at 78. Dr. Shane stated that the cerebral edema associated with Sudden Infant[, which] is usually due to some [prior] hypoxia[,] . . . [is] different from . . . vasogenic edema." Id. at 78-79. "[T]he extent of cerebral [edema] in Sudden Death–because it is sudden . . . [is] usually extremely small–it's minimal to very, very mild." Id. at 79. Additionally, Dr. Shane stated, "lung changes" can occur. Id.

In response to Dr. Shane's assertions, Dr. Gilbert-Barness testified that what is now known about "Sudden Infant Death Syndrome as it is called . . . [is] that many of these deaths [were] very likely related to the [sleeping] position . . . and . . . the hazards of mattresses, beds and bedding." Tr. at 123. Certain bedding and sleeping conditions create an environment that increases the likelihood of Sudden Infant Death that is related to an asphyxial death. See Tr. at 121-124, 126 ("[W]e know now . . . that most of these deaths are due to [sleeping] position and [are] related to an asphyxial death."). Dr. Gilbert-Barness testified that "one of the most important things in defining [the cause of] SIDS is [the] examination of the death scene."[31] Tr. at 124. (Noting that Child Doe/11 was not in the prone position but that she was lying on a pillow, see Tr. at 126, noting that Child Doe/11 "was on a couch with her father who was many times her size, and there were pillows on the couch," see Tr. at 123, and noting that Child Doe/11 "could have rolled to the side and then asphyxiated," see Tr. at 126, Dr. Gilbert-Barness expressed the view that Child Doe/11's nap environment put her at risk to suffer a sudden infant death by means of asphyxiation, see Tr. at 123-124, 126.

In addition to the conditions at the death scene, the pathological changes that were observed microscopically in Child Doe/11 informed Dr. Gilbert-Barness's opinion. She stated:

> There were petechial--epicardial petechial hemorrhages which are small, pinpoint hemorrhages from the membrane that covers the heart. There was marked congestion of the abdominal organs which Dr. Shane has mentioned. There was over-distinction of the alveoli of the lungs, and there

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[31] Dr. Gilbert-Barness stated that she doesn't "like using the term Sudden Infant Death Syndrome because it's not really a syndrome . . . . In fact, it is Sudden Infant Death, cause not determined, if you can call it SIDS–or [it is Sudden Infant Death by] what the cause actually is." Tr. at 126 (emphasis added).

were---some mild increase in the smooth muscle of the pulmonary arteriole--in the brain. And all of these features are certainly consistent with Sudden Infant Death [caused by asphyxia].

Tr. at 124.

The filed literature confirms the testimony of both experts concerning the type of findings associated with a death initially diagnosed as a SIDS death, but after further examination of the circumstances of the death, is found to be a death that can be explained, whether by "major disease entities that mimic SIDS in presentation," see R's Ex. FF at 2 (M. Valdes-Dapena, M.D., Sudden Infant Death Syndrome: Pathologic Findings, Clinics in Perinataology, Vol. 19, No. 4 (Dec. 1992)), or by other explanation (which includes accidental asphyxiation), see id. at 6. In such circumstances, although the death may be referred to as a SIDS death with explanation (or an explained SIDS death), the cause of death is no longer unknown as in the case of the classically defined SIDS death "which remains unexplained after a thorough case investigation." See id.; see also Ps' Ex. 20 at 481.

The pathological findings during a typical SIDS autopsy were described during the first international conference on the causes of sudden infant death, which was held in Seattle, Washington, in 1963. R's Ex. FF at 3. Those findings have been described consistently in subsequent studies of both explained and unexplained SIDS deaths. See id. at 3-7.

Among the noted findings, based on an examination of brains that have come from infants who were noted to have died from sudden infant death syndrome, is a finding that many of the examined brains exceed the ninety-ninth percentile in brain weight. See R's Ex. MM at 1 (H. Kadhim, et al., Incongruent Cerebral Growth in Sudden Death Infant Death Syndrome, Journal of Child Neurology, Vol. 20, No. 3 (March 2005) (57% of the examined brains from the SIDS victims were above the 99th percentile for brain weight)); see also R's Ex. KK at 9 (F. J. Aranda, Assessment of Growth in Sudden Infant Death Syndrome, Neuroepidemiology, Vol. 9, (1990) (another study reporting 81% of the examined brains of SIDS infants were above the 95th percentile for brain weight, including 19% above the 99.9th percentile)). Although the brain weights were heavy, cerebral edema, if present at all, was noted in a minority of the examined brains. R's Ex. MM at 1 (cerebral edema was noted in only 14% of examined brains); see also R's Ex. KK at 9 (noting that the studied series of SIDS children "did not show macroscopic or histologic evidence of brain edema or ventricular dilatation which might have accounted for the increased brain size"). The weight of the other vital organs, including the liver, lungs, and heart, also tended to be elevated. See id. The researchers found that the brain

weight "correlated closely" with total body weight. Id.; see also R's Ex. KK at 193 (observing that "not only were the brains large, but the children were also tall for their ages").

Other "classic findings" that "are apt to be observed in the course of a typical postmortem examination in a case of SIDS" include, among other internal findings: (1) petechiae in the thymus, pleura, and pericardium, (2) pulmonary congestion and edema, and (3) an empty urinary bladder. R's Ex. FF at 3 (M. Valdes-Dapena, M.D., Sudden Infant Death Syndrome: Pathologic Findings, Clinics in Perinataology, Vol. 19, No. 4 (Dec. 1992)).

Many of the classic findings in a post mortem examination of a SIDS case were present in Child Doe/11 at autopsy. She was a long, weighty baby with a large brain. Although there was evidence of some edema in her brain, because edema of the degree that Dr. Shane asserted was present in Child Doe/11 is accompanied generally by clinical symptoms of a severity and type that were not present in this case, see supra Part III(B)(2)(a)(iii)(A), the undersigned is not persuaded that the edema was as severe as Dr. Shane described.

With respect to Child Doe/11's other organs which were also heavy, Dr. Shane testified during the hearing that he did not see edema in those organs. See Tr. at 103-104. Even though Dr. Shane admitted that he saw no evidence of edema in those organs, he yet asserted that edema must have been present to account for the heaviness of Child Doe/11's organs and to support petitioners' causation theory of a cytokine-induced encephalopathy. See id. at 104.

Child Doe/11's autopsy report reflects that she had rare epicardial petechiae, that she had pulmonary congestion and edema, and that she had an empty bladder. Moreover, the testimony of petitioners describing the circumstances surrounding Child Doe/11's death and the particulars of her sleeping position on the futon with her father supply an explanation for the death. The parties' experts offered different opinions regarding the likelihood of Child Doe/11's death being a respiratory one. Dr. Shane stated that in the absence of an active upper respiratory infection, a history of respiratory difficulties, abnormal pulmonary findings, and the "expected pathologic findings" for SIDS deaths, Child Doe/11's "case represent[ed] an encephalopathic death." Ps' Ex. 11 at 2 (Dr. Shane's report). Dr. Gilbert-Barness, however, stated that the pathological findings at autopsy and the circumstances surrounding Child Doe/11's death, in particular, as described by John Doe/11, that Child Doe/11 was lying on a pillow propped up on a futon next to her father so that he could cuddle with her, militated in favor of a finding that Child Doe/11 died as a result of a sudden infant death with an explanation, in particular,

an accidental mechanical asphyxiation.[32]

The undersigned considered, as a whole, the testimony of petitioners and of the parties' experts regarding Child Doe/11's clinical and pathological presentation (including the experts' discussion about the expected pathological findings in an explained SIDS death), the filed medical literature and the medical records in evaluating whether petitioners' medical theory reflected a logical sequence of cause and effect supported by a reliable medical explanation. The testimony of respondent's experts and the literature filed by respondent's experts exposed the difficulties with petitioners' proposed theory. See DeBazan v. Sec'y of Dept. of Health and Human Servs., 539 F.3d 1347, 1353 (Fed. Cir. 2008) (providing that "[t]he government, like any defendant, is permitted to offer evidence to demonstrate the inadequacy of petitioners' evidence on a requisite element of petitioners' case-in-chief"). Although some of the testimony and literature supplied by respondent might also have advanced a claim of alternate causation by respondent if petitioners had prevailed in proving a prima facie case, the undersigned considered the aspects of the offered evidence (including that offered by respondent) for the limited purpose of evaluating carefully the reliability of the medical underpinnings of petitioners' proposed causal sequence for a vaccine injury.

Here, petitioners' proposed sequence of post-vaccinal events that led to an encephalopathy does not appear to be supported by the facts of the case. Dr. Shane's opinion of causation rested heavily on his view that Child Doe/11's brain was heavy and that heaviness necessarily indicated that Child Doe/11 had moderate to moderately severe edema, see Tr. at 12, and the opinion of petitioners' expert, Dr. Levin, rested as well on a finding of significant edema in Child Doe/11's brain based on Dr. Shane's opinion of

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[32] Dr Gilbert-Barness testified about the different methods of accidental mechanical asphyxiation and filed medical literature addressing the various means by which a child might suffer accidental mechanical asphyxiation. See Tr. at 121, 123, 126; see also R's Ex. NN (K. Collins, M.D., Death by Overlaying and Wedging, a 15 year Retrospective Study, The American Journal of Forensic Medicine and Pathology, Vol. 22 (2001)). The discussed methods of accidental mechanical asphyxiation were overlaying and wedging. See R's Ex. NN at 3. Overlaying occurs when an infant is pressed into the bedding or the clothing of a sleeping adult and either the infant's face is covered or the sleeping adult compresses the infant's thorax or abdomen. See id. at 5. Wedging "occurs when an infant's body or face is compressed within a narrow space, resulting in asphyxia from interference with chest wall movements or obstruction of airway." Id. at 6. Autopsy findings of intrathoracic petechiae may occur in SIDS deaths for which there is no explanation after a thorough examination of the circumstances surrounding the death. Id. at 4. However, autopsy findings of intrathoracic petechiae are "often viewed as signs or indicators of asphyxial death." Id.

Child Doe/11's pathology, see Tr. at 198, 203 (referencing Ps' Ex. 22[33] at 5 (an excerpt from Nelson's Textbook of Pediatrics) (explaining that inflammation in the brain can lead to increased intracranial pressure [ICP], and that increased ICP can be "due to cell death (cytotoxic cerebral edema) [or to] cytokine-induced increased capillary vascular permeability (vasogenic cerebral edema)"). In the absence of clinical symptoms of the type and severity that would be expected medically in circumstances in which the pathological picture was as dire as petitioners' experts described, however, the undersigned is not persuaded that Child Doe/11's pathological presentation was, in fact, as critical as petitioner's experts have asserted. Because the undersigned finds that petitioners have not carried their burden of proving that Child Doe/11's brain was significantly edematous, an important aspect of petitioners' proposed sequence of cause and effect, petitioners do not prevail on the second prong of the Althen standard.

Nonetheless, for the sake of completeness, the undersigned addresses the aspect of petitioners' proposed sequence of cause and effect in support of which petitioners presented the testimony of Dr. Levin, petitioners' immunology expert. Dr. Levin opined that Child Doe/11's received hepatitis B vaccination triggered a cytokine storm that led to brain edema, encephalopthy and, ultimately, death. See Ps' Ex. 12 at 4 (Dr. Levin's report); Tr. at 201-215.

b. Whether Child Doe/11's received hepatitis vaccination triggered a cytokine storm that led to an encephalopathy and, in turn, Child Doe/11's death

Dr. Levin concurred with Dr. Shane that Child Doe/11's death was caused by her receipt of the hepatitis B vaccination. Dr. Levin opined in his report that Child Doe/11's vaccination led to an "excessive cytokine release followed by cerebral edema." Ps' Ex. 12 at 4. Dr. Levin explained that cytokines

> regulate the rate at which certain proteins are created or certain proteins aren't created. They control the body. . . . [C]ytokine are very, very much responsible for, among other things, inflammation, and that means that . . . when the body gets attacked by something–toxic chemical, virus or bacteria–then the body creates the reaction of inflammation.

Tr. at 199-200. According to Dr. Levin's cytokine theory, increased cytokine levels contribute to increased water content in the brain around blood vessels, a condition

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[33] The reference in the transcript is actually to petitioners' exhibit 17.

known as vasogenic edema. See Tr. at 203-204 (referencing Ps' Ex. 22[34] (an excerpt from Nelson's Textbook of Pediatrics describing cytokine-induced brain edema)). Edema in the brain results in a decreased blood flow, which can lead to death. See id.

Dr. Levin submitted literature in support of his theory that hepatitis B is a superantigen that is capable of triggering a cytokine storm. In particular, Dr. Levin provided an excerpt from the Institute of Medicine Report filed as Petitioners' Exhibit 26 (The Institute of Medicine, Board on Health Promotion and Disease Prevention, Immunization Safety Review: Hepatitis B Vaccine and Demyelinating Neurological Disorders (The National Academies Press 2002)). The excerpt described superantigens as

> proteins that are produced by viruses and bacteria and that activate T cells either by direct activation of auto-reactive T cells (regardless of antigen specificity) or activation of humoral responses. Superantigens can also lead to the release of inflammatory mediators such as cytokines, which could participate in demyelinating processes. It is conceivable that antigenic stimulation from vaccines generally, and from hepatitis B vaccine in particular, could trigger [any] one of three posited mechanisms [leading to demyelination]." Thus, there is a theoretical basis for an association between vaccine-induced immune response and demyelination. Biological evidence exists regarding some components of this theory.

Ps' Ex. 26 at 2 (emphasis added by petitioners). The IOM report on which Dr. Levin relies, however, postulates a theoretical basis for an association between a vaccine-mediated immune response and demyelination (a process involving the destruction, removal or loss of the myelin sheath surrounding nerves). The report does not address an association between a vaccine-mediated inflammatory response and cerebral edema.

Respondent's expert witnesses refuted petitioners' claim that Child Doe/11 had suffered a vaccine-related injury. As discussed earlier in this decision, see supra Part II(B)(2)(a)(ii), Dr. Gilbert-Barness disputed Dr. Shane's finding of significant cerebral edema in Child Doe/11. Both Dr. Gilbert-Barness and Dr. McCusker opined that the symptoms that Child Doe/11 exhibited after her immunization were not encephalopathic, see Tr. at 139, 264-265, and Dr. McCusker disputed the plausibility of Dr. Levin's proposed biological mechanism in this case. In particular, Dr. McCusker challenged the aspect of petitioner's theory advanced by Dr. Levin that a cytokine storm had occurred.

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[34] The reference in the transcript is actually to petitioners' exhibit 17. The same excerpt, however, is also filed as petitioners' exhibit 22. Having referred to petitioners' exhibit 22 earlier in this decision, the undersigned continues to refer to this exhibit number for consistency.

Before turning to the points of disagreement between the parties' expert immunologists, the undersigned first reviews the points of agreement between the experts.

Dr. Levin stated that the hepatitis B vaccination "is designed" to cause a cytokine reaction. Tr. at 201-202. Dr. McCusker agreed, explaining that the purpose of a vaccination is to activate an immune response that "require[s] the formation of T-cells[, which generate cytokines,] . . . that are specific for th[e] [foreign] protein . . . as well [as] the formation or the activation of B-cells to ultimately form antibodies."[35] Tr. at 244, see also 247 (Dr. McCusker).

Dr. Levin testified that "cytokine-induced reactions [include] fever, local pain, swelling, [and] the like." Tr. at 202. Moreover, Dr. Levin explained that the difference between cytokine activation and a cytokine storm was "a matter of degrees. . . . [A]ctivation can be a normal phenomenon[.] . . . [T]he storm [is worse]." Tr. at 225.

Dr. McCusker did not disagree. Describing the different types of cytokines, Dr. McCusker stated that proinflammatory cytokines are "designed to ramp up the system and call the effector cell[s] – the cells and the proteins that are going to do something to that antigen – to that bacteria that you're infected with." Tr. at 248. Id. Proinflammatory cytokines "open up the spaces . . . between the blood vessels so that cells that are sitting in the tissue can come into the blood vessel[s] and be directed to the site of inflammation or to the site of attack." Id. at 249. These are the cytokines that "can increase temperature, [and that] can give you a sense of malaise, that sense of 'I feel lousy.'" Id. at 250. Dr. McCusker acknowledged that cytokine activation can cause a headache in connection with the systemic effects of fever and malaise that occur as part of a normal response to an induced cytokine reaction, but she made clear that "a headache is not cerebral edema." Id. at 250. Dr. McCusker explained that normal immune responses involve the release of cytokines, but "when cytokines . . . get out of control, we call it cytokine storm." Id.

The parties' experts agreed that normal cytokine activation is not the same as an induced cytokine storm. A cytokine storm involves a much more intense and serious reaction of the immune system than occurs with normal cytokine activation.

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[35] Among the multiple functions of the T cells is the generation of cytokines. Lauren Sompayrac, How the Immune System Works at 8-9 (2d ed. 2003). The B cells of the immune system produce antibodies. Id. at 28.

The parties' immunology experts diverged in their opinions on other aspects of petitioners' proposed causal sequence. Specifically, the parties' experts disagreed on the distances over which cytokines act to produce a significant cytokine reaction and the symptoms that are indicative of a significant cytokine reaction.

Dr. Levin testified that "anything that induces cytokines in the periphery [of the body] - even in the big toe - can cause symptoms in the head. Tr. at 210 (quoting in part the 2000 Yokota article, filed as R's Ex. Q at 4, for the proposition that "[a]lthough the C[entral]N[ervous]S[ystem] has long been an immunologically privileged organ, . . . findings indicate that there exists a pathway and mechanisms for cytokine signaling in the CNS").[36] He described the "classic situation[]" in which cytokines in the body's periphery cause central nervous system problem is the situation in which an abscess in a big toe causes a headache. Tr. at 210. Additionally, relying on several sentences in the 2005 Tonelli article, filed as R's Ex. W, that describe "the induction of cytokine production by cells of the brain in response to the activation of the immune system in the periphery" as one of the mechanisms by which an inflammatory response in the brain may be generated, Dr. Levin asserts that "the shot in [Child Doe/11's] leg can easily cause cerebral edema."[37] Tr. at 215.

The 2000 Yokota article, filed as R's Ex. Q and referenced by Dr. Levin, addressed the possible mechanisms by which an influenza virus caused "uncontrolled immune reactions in the brain" that manifested as an acute encephalopathy, R's Ex. Q at 2, and that preceded a "systemic progression to the failure of multiple organs," R's Ex. Q at 3. Although it was unclear to the researchers how the virus infected the brain, R's Ex. Q at 2, it appeared that the "uncontrolled immune reactions in the brain" resulted from a viral infection within the brain and not, as Dr. Levin suggested during his hearing testimony, from cytokine activation in the body's periphery.

Moreover, the 2005 Tonelli article, which was filed as R's Ex. W and referenced during the hearing by Dr. Levin, addressed "the transient depressed mood, anxiety, and cognitive impairment" that resulted in cases of cytokine production in the brain that

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[36] The article filed as R's Ex. Q is: Shumpei Yokota, et al., Hypothetical pathophysiology of acute encephalopathy and encephalitis related to influenza virus infection and hypothermia therapy, 42 Pediatrics International 197-203 (2000).

[37] The article filed as R's Ex. W is: Leonardo H. Tonelli, et al., Tumor Necrosis factor alpha, interleukin-1 beta, interleukin-6 and major histocompatibility complex molecules in the normal brain and after peripheral challenge, Vol. 27, Neurological Research (Oct. 2005).

occurred in response to inflammation in the body's periphery (a peripheral activation of the body's immune responses). See R's Ex. W at 3, 5 (emphasis added). The noted systemic immune response that extended to the brain did not include the deleterious inflammatory response of significant edema that Dr. Levin posited had occurred in Child Doe/11's case.

Dr. McCusker interpreted the literature that she filed in support of her opinion differently than Dr. Levin, and she disagreed with Dr. Levin's proposition that the vaccination in Child Doe/11's leg could have led easily to a cytokine storm and, in turn, to cerebral edema. As Dr. McCusker explained in her report, pro-inflammatory cytokines "function to increase inflammation at the site of infection." R's Ex. C at 2. As Dr. McCusker further explained during her hearing testimony, the effects of pro-inflammatory cytokines that increase vascular permeability or produce cerebral edema are immune responses that are "directed to the site of inflammation or the site of attack." Tr. at 250. Such immune responses "are effects that can only occur locally . . . [but] do not occur over long distances." Id. at 250 (emphasis added).

In contrast, cytokines that can "act across distances are really tightly regulated . . . [and] don't have that many jobs across distances." Id. at 249. Among the cytokines that can act across distances are the cytokines which are released to have systemic effects that include triggering a fever and causing malaise or sleepiness. Tr. at 251; see also R's Ex. C at 4. Cytokine activation and inflammation in the body's periphery can result in the expression of pro-inflammatory cytokines in the brain. R's Ex. C at 4 (citing the 2005 Tonelli article which was filed as R's Ex.W). But that expression does not involve "life threatening inflammation." Id. Dr. McCusker stated that in addition to the limited systemic effects that cytokines generate over distances, there is a limited period of time within which cytokines can act in the body. See Tr. at 251-252 (Dr. McCusker stating that "cytokines . . . don't hang out in the body for very long" and pointing to one cytokine, TNF-Alpha,[38] the half-life of which is 15 minutes").

Moreover, to prevent the detrimental effects of excessive inflammation, cytokine reactions are moderated by the release of anti-inflammatory cytokines (or regulatory cytokines) at the same time that the immune system releases pro-inflammatory cytokines. Id. at 252; see also R's Ex. C at 2 (describing the body's feedback mechanism to regulate

[38] TNF-[alpha] is tumor necrosis factor-alpha, an "alarm" cytokine "which signal[s the immune system] that an invasion has begun." Lauren Sompayrac, How the Immune System Works (2d ed.) at 20. Among the pathological conditions that TNF-alpha can induce is systemic inflammatory response syndrome. R's Ex. Q at 200.

pro-inflammatory responses). Based on these various regulatory factors, Dr. McCusker testified that the side effects of an immune response are minimized in most circumstances. Tr. at 252.

Discussing the release of cytokines in the context of vaccinations, Dr. McCusker explained that a vaccination induces an immune response that has local effects, specifically, "redness, swelling and pain at the [injection] site." Tr. at 251. The effects acting over longer distances include fever and somnolence. Id. Returning to Dr. Levin's example of the gentleman with an abscess in his big toe and a headache, Dr. McCusker stated that the headache "may be an effect of the cytokine[s], but his headaches is not cerebral edema. [Rather,] his headache is the fever and malaise that's being induced by the cytokine[s]." Tr. at 250.

As additional support for her challenge to Dr. Levin's proposition that the vaccination in Child Doe/11's leg led to a cytokine storm that resulted in her cerebral edema, Dr. McCusker pointed to R's Ex. DD,[39] an article that describes an immune response that gets "out of control" which is "what happens in a cytokine storm." Tr. at 252, 254, see also R's Ex. DD at 9 (The clinical data obtained during the phase 1 trial of a study drug "provide[d] insight into the natural course of [a] cytokine storm and [a] systemic inflammatory response."). In the phase 1 clinical trial of a particular study drug, healthy volunteers received an intravenous infusion of the study drug that produced "a sudden and rapid release of proinflammatory cytokines." Id. The design of the study drug permitted direct and enhanced stimulation of the immune system. See id. at 1. After an hour, the volunteers reported the development of a severe headache. Id. at 2. Restlessness, nausea, vomiting, bowel urgency and diarrhea followed within the first couple of hours after the intravenous infusion. Id. Within four hours after the received infusion, the volunteers had rapid heartbeats and a drop in blood pressure. Id. Although one volunteer exhibited signs of respiratory failure, marked by rapid breathing, five hours after his infusion, evidence of marked respiratory distress and low blood pressure in another of the volunteers twelve hours after the infusion caused the researchers to transfer the volunteers to critical care. See id. at 2, 4-5. Between sixteen to twenty hours after the infusion, all of the volunteers had signs of tachypnea ("excessive rapidity of breathing," Dorland's at 1851). R's Ex. DD at 9. Evidence of renal impairment followed. R's Ex. DD at 5, 9. The multi-organ failure occurred "over the course of several days." Tr. at 254; R's Ex. DD at 10. Having described a progression of systemic effects that typifies

[39] The article filed as R's Ex. DD is: Ganesh Suntharalingam, et al., Cytokine Storm in Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412, Vol. 355(10), New England Journal of Medicine 1018-1028 (Sep. 7, 2006).

the course of a cytokine storm, Dr. McCusker observed that none of these systemic effects appeared in the case of Child Doe/11. See Tr. at 255, 259.

While Dr. McCusker acknowledged that pro-inflammatory cytokines can participate in the development of cerebral edema, see R's Ex. C at 4; Tr. at 257, she testified that cytokine-induced cerebral edema has been shown to develop only in situations where the tissue in or around the brain has been infected or compromised by viruses, see R's Ex. C at 4 (Dr. McCusker's report); Tr. at 256; R's Ex. Q at 197. In the absence of a direct infection of the brain tissue, there has been no showing that immune responses to either bacteria or viruses have caused either a cytokine storm or cerebral edema. R's Ex. C at 4; Tr. at 258. Nor has the occurrence of a cytokine-induced cerebral edema been reported following either wild hepatitis B infection or the administration of the hepatitis B vaccine. R's Ex. C at 4; Tr. at 279-80, 282.

Dr. McCusker testified that because many cytokines are involved in the regulation of immune responses and the cytokines "don't feed off one another" but "act independently," it is "really difficult" for a "rogue cytokine" to throw the immune system out of control and generate a cytokine storm. Tr. at 272-273. She added that the filed literature indicates that a devastating cytokine storm occurs in those circumstances where the system is overwhelmed with infection. Id. at 273.

Based on what has been observed and reported in the literature, Dr. McCusker asserted that any significant release of pro-inflammatory mediators that is sufficient to create a cytokine storm results first, in the onset of fever, as an initial symptom, and then, frequently leads to multi-organ failure. R's Ex. C at 4; Tr. at 254-55; see also, 259-60, R's Ex. DD. Dr. McCusker explained that multi-organ failure is characterized by "cellular infiltrates" and "more evidence of inflammation." Tr. at 260. The inflammation involved in multi-organ failure is a "very, very regulated" process by which there is an "increase in vascular permeability, the influx of cells to the area, and the release of mediators to increase inflammation and to inevitably result in the death of the organism that you are trying to attack." Id. at 261. Because no fever was reported in this case, and Dr. Anthony's examination of Child Doe/11's internal organs at autopsy was unremarkable for multi-organ failure (as marked by "cellular infiltrates" and "more evidence of inflammation"), Dr. McCusker opined that there is a causal "disconnect" between the vaccination and Child Doe/11's death.[40] R's Ex. C at 4; Tr. at 259-261.

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[40] On cross-examination of Dr. McCusker, petitioners' counsel inquired about the one reference in the record to Child Doe/11's temperature. See Tr. at 299. The note to which petitioner's counsel referred is in the narrative section of the emergency responder's Patient Care Report. Ps' Ex. 4 at 1. The note states, in pertinent part, "pt. had ⊖ pulse ⊖ resp ⊖ heart tones,

The undersigned found Dr. McCusker's testimony which challenged Dr. Levin's proposed "sequence of cause and effect," specifically that Child Doe/11's death was the result of a cytokine-induced cerebral edema, or "cytokine storm" caused by the hepatitis B vaccine, more persuasive on the facts of this case. Dr. Levin's opinion requires, as a predicate to support his theory that Child Doe/11 suffered an acute encephalopathy after her vaccination, a pathological finding that Child Doe/ 11's organs were significantly edematous at her death. The necessary pathological findings to support Dr. Levin's proposed causation sequence, however, are lacking in this case. Moreover, the literature filed in this case provides evidence that a systemic cytokine reaction that results in cerebral edema is accompanied by multi-organ failure as well. In the absence of evidence of significant cerebral edema or evidence of multi-organ failure in Child Doe/11, the likelihood is diminished that she suffered a systemic cytokine reaction that precipitously led to her death before the appearance of any of the significant symptoms (either clinically or pathologically) that are indicative of an occurring cytokine storm. Petitioners have failed to establish a logical sequence of cause and effect supporting the cytokine storm aspect of their theory of causation.

3. Proximate Temporal Relationship Between the Vaccination and Child Doe/11's Death

The third prong of the Althen standard requires that petitioners establish an appropriate temporal association between the vaccination and the injury. Althen, 418 F.3d at 1278. Petitioners allege that Child Doe/11's death resulted from an encephalopathy caused by a vaccine-induced cytokine storm. As discussed in Part III(B)(2) of this ruling, the facts of this case do not support a finding that Child Doe/11 suffered an encephalopathy or that a cytokine storm occurred. For the sake of completeness, however, the undersigned addresses the timing issue. Here, the parties' immunology experts disagreed on the timing required for a significant cytokine reaction (or cytokine storm) to occur.

Dr. Levin testified that "cytokine activation" is "effected within seconds" and that an "actual cytokine storm that translates into multi-organ failure is also effected within seconds," but the development of the storm and the presentation of the related symptoms

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skin was warm, dry." Id. In the context of all of the records documenting Child Doe/11's medical attention after her father found her "bluish" on the futon, the undersigned views the note as a general comment on Child Doe/11's perimortem skin temperature and not an indication of a feverish state. Compare Ps' Ex. 4 at 1 ("pt. had ⊖ pulse ⊖ resp ⊖ heart tones, skin was warm, dry") with Ps' Ex. 5 at 3 (emergency room assessment note that Child Doe/11 "asystolic on arrival, cold, cyanotic").

occurs "hours out." Tr. at 308. Dr. Levin then clarified his testimony stating that when defining "cytokine storm as a clinical condition" . . . .it doesn't happen immediately. . . . It depends on the person, but I would say that seven hours is totally reasonable." Tr. at 310-311. He pointed out that "in this particular child's case it took–what, eight hours or something like that." Tr. at 308. Subsequently, when questioned by petitioners' counsel, Dr. Levin shortened the reasonable time frame to three hours.

The pertinent testimony was as follows:

By petitioners' counsel, Mr. Gage:

Q: I just want to be clear on this last point, Dr. Levin. We have stipulated that the shot was given at 2:00, and the call to the ambulance was at 6:47 or 6:49, so that would have been four hours–four and a half hours, something like that. You said seven hours was reasonable. In the context of this case specifically, we need to know whether four hours or four and a half hours is reasonable.

A: Yes, four and a half hours is reasonable.

Q: Okay.

The Court: Three hours - because that would have been -

The Witness: Three hours is also reasonable.

The Court: Three hours?

The Witness: I mean, 10 minutes - well, in this particular situation [apparently referring to R's Ex. DD] when the people fell over from the cytokine storm that they got, the problem was that the protocol called for each person to get an injection 15 minutes after the first one did, and the investigator - given that the animals did not have an adverse reaction - decided to inject everybody at the same time. So by the time the seventh guy was injected, which is 15 minutes times seven which is what - two hours, two and a half hours - the first guy had fallen out - he passed out 'cause he was in shock. And so that was two and a half hours, and that was a massive, massive, massive reaction. So yeah - and this was in healthy adults, and they were screened to be healthy. They weren't newborns. They were screened to be healthy. They went through a clinical intake

protocol, so they had great cardiovascular systems, great everything, within two hours, two and a half hours, this guy was in a real serious storm.

The Court: Thank you, Dr. Levin.

Mr Gage: Okay, thanks. That's good.

Tr. at 311-312.

The study to which Dr. Levin referred during this testimony was R's Ex. DD. As discussed in Part III(B)(2)(b) of this decision, the article described the infusion procedure of a study drug that produced a rapid release of pro-inflammatory cytokines, the initial response after infusion and subsequent events. The article addressed the timing of the events in detail. "[E]ach volunteer received an intravenous infusion, 10 minutes apart, of either the study drug or placebo. Each infusion lasted 3 to 6 minutes." R's Ex. DD at 2. The investigators reported a series of adverse events that began in the treatment group after the infusion, describing both the adverse event and the time frame within which the event appeared. The onset of the first reported adverse event, severe headache, occurred "after a median of 60 minutes (range, 50 to 90 [minutes]), accompanied by lumbar myalgia in all six patients [who received the study drug] after a median of 77 minutes (range, 57 to 95)." Id. The investigators reported that during this early phase, the patients were restless and had varying degrees of nausea, vomiting, bowel urgency or diarrhea. Id. Although the investigators did not report the time during which these symptoms appeared, the undersigned construes the "early phase" to mean the first two to three hours after infusion because the investigators reported that all of the patients experienced "[h]ypotension (defined as a decline in systolic blood pressure of 20 mm Hg or more) . . . a median of 240 minutes (range, 210 to 280) [or four hours] after infusion, accompanied by tachycardia [rapid heartbeat], with maximal heart rates of 110 to 145 beats per minute. Id. The first patient who had received the infusion exhibited signs of respiratory failure, signalled by excessively rapid breathing (tachypnea), "300 minutes [or five hours] after infusion." Id. The marked respiratory distress and hypotension (low blood pressure) observed in one of the volunteers "12 hours after infusion" precipitated the transfer of the patients to critical care. Id. at 4-5. As reflected in Table 1 of R's Ex. DD, all of the patients required transfer to critical care between 12 to 16 hours after infusion. See R's Ex. DD at 3; see also Tr. at 290 (Dr. McCusker pointing to R's Ex. DD to support the proposition that the presentation of multi-organ failure would require, at least, 12 to 16 hours).

The underlying factual data in the article filed as R's Ex. DD, on which Dr. Levin relied to support his view of the time frame within which the clinical presentation of a

cytokine storm could be expected to appear, does not support the compressed time frame that Dr. Levin proposed. The patient who exhibited signs of respiratory failure five hours after the infusion of the study drug had shortness of breath. Prior to that occurrence and approximately four hours after their infusions, the patients became restless and then experienced a drop in blood pressure which was accompanied by a rapid heartbeat. Petitioners described no restlessness or shortness of breath in Child Doe/11 in the hours following her vaccination. Neither did Child Doe/11 manifest any of the other described symptoms that present first when a cytokine storm is underway. Although, as petitioners' counsel asked of respondent's expert, Dr. McCusker, on cross-examination, Child Doe/11 did not live twelve hours after the receipt of her vaccination, neither did she manifest any of the anticipated symptoms of a developing cytokine storm within the four and half hours between her vaccination and her bluish appearance to her parents.

Challenging Dr. Levin's testimony, Dr. McCusker testified that the timing of Child Doe/11's death from a cytokine-storm mediated edema was "too soon." Tr. at 258; see also R's Ex. C at 5. Reports of cerebral edema following infection of nervous tissue generally are accompanied by fever and significant symptom development usually requires several days to occur. Respondent's Ex. C at 5. see also Tr. at 258 (Dr. McCusker stating that "case reports of encephalopathy induced by different organisms . . . [indicate] that the progression occurs over days. It doesn't happen over hours. It takes days for there to accumulate enough edema for . . . the final event [of death] to occur.").

Although petitioners' expert, Dr. Levin, offered an opinion that three or four hours was a reasonable period of time for the manifestation of the clinical symptoms of a cytokine storm to appear, Child Doe/11 did not manifest any of the anticipated symptoms within that time frame. The lack of clinical symptoms within the expected time frame does not support a finding in petitioners' favor regarding the causal relationship between Child Doe/11's vaccination and her death. In the absence of clinical and pathological evidence that a cytokine storm had occurred or that an encephalopathy had resulted, the undersigned is not persuaded by petitioners' theory that Child Doe/11's sleepiness during the several hours after her vaccination was indicative of an abnormal vaccine reaction that ultimately led to her death. It appears to the undersigned that the timing of Child Doe/11's death was too soon to have resulted from a cytokine storm. See DeBazan, 539 F.3d at 1352 (upholding a decision in a case in which "onset is too soon" because the "temporal relationship is not such that it is medically acceptable to conclude that the vaccination and the injury are causally linked").

III. Conclusion

For the foregoing reasons, the undersigned concludes that petitioners' theory of

causation connecting Child Doe/11's vaccination to her death is not supported by the facts of Child Doe/11's case. Accordingly, the undersigned finds that petitioners have not satisfied their burden of proof under the Althen standard and have not established an entitlement to Vaccine Program compensation. The Clerk of the Court shall **ENTER JUDGMENT** accordingly.[41]

IT IS SO ORDERED.

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Patricia E. Campbell-Smith
Special Master

[41] Pursuant to Vaccine Rule 11(a), entry of judgment is expedited by the parties' joint filing of notice renouncing the right to seek review.