In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. XX-XXXV
Filed: July 26, 2010

JANE DOE/78 and JOHN DOE/78, Natural Parents and Guardians of CHILD DOE/78, a minor,	)	PUBLISHED
Petitioners,	)	Entitlement; Prevnar; Diphtheria-Tetanus-acellular Pertussis;
v.	)	Hemophilus influenzae type b; Herpes simplex encephalitis;
SECRETARY OF HEALTH AND HUMAN SERVICES,	)	Causation-in-fact; cytokines
Respondent.	)	

Carol L. Gallagher, Gallagher & Gallagher, Somers Point, NJ, for Petitioners.
Darryl R. Wishard, U.S. Department of Justice, Washington, D.C., for Respondent.

DECISION[1]

LORD, Chief Special Master.

I. INTRODUCTION AND OVERVIEW

Petitioners JANE and JOHN DOE/78 ("Petitioners") filed this case under the National Childhood Vaccine Injury Act ("Vaccine Act"), 42 U.S.C. § 300aa-10 et seq., on behalf of their daughter, CHILD DOE/78 ("Doe"). Petitioners allege that the Prevnar, Diphtheria-Tetanus-acellular Pertussis ("DTaP"), and Hemophilus influenzae type b ("Hib") vaccines administered on May 2, 2007, caused Doe to contract herpes simplex encephalitis ("HSE"), resulting in neurological injuries. Petitioners do not allege that Doe suffered an injury on the Vaccine Injury Table and therefore must prove that the vaccinations in fact caused Doe's injuries. See § 300aa-

[1] As provided by Vaccine Rule 18(b), each party has 14 days within which to request the redaction "of any information furnished by that party (1) that is trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Rules of the United States Court of Federal Claims (RCFC), Appendix B, Vaccine Rule 18(b). In the absence of a timely motion, the entire document will be made publicly available.

14; 42 C.F.R. § 100.3(a).

To prove an off-Table claim, a petitioner must provide evidence, in the form of medical records or reliable medical opinion, to establish "(1) a medical theory causally connecting the vaccination to the injury, (2) a logical sequence of cause and effect showing the vaccination was the reason for the injury, and (3) a proximate temporal relationship between the vaccination and the injury." Althen v. Sec'y of Dep't of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005).

In this case, all the parties and experts agree that (1) Doe contracted a herpes simplex viral infection, (2) she did not contract herpes directly from the vaccinations, (3) she developed HSE shortly after she received vaccinations on May 2, 2007, (4) the evolution of her condition was perfectly congruent with HSE, and (5) HSE caused her neurological injuries. The issue is whether Doe's vaccinations caused or exacerbated her herpes infection by weakening her immune system.

After carefully evaluating and weighing all of the evidence, the undersigned finds that Petitioners have not satisfied their burden of making a prima facie case under Althen. Specifically, Petitioners have not presented a coherent medical theory demonstrating that vaccines can increase vulnerability to herpes simplex infection or exacerbate such infection. With the clear understanding that a plausible theory of general causation need not be confirmed by laboratory results or epidemiological studies, the fact remains that, in the absence of such confirmation, the theory must at least have a basis in a medical expert's scientific knowledge or experience. See Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 590 (1993) (requiring "more than subjective belief or unsupported speculation"); see Terran v. Sec'y of Dep't of Health & Human Servs., 195 F.3d 1302, 1316 (Fed. Cir. 1999) (approving use of Daubert to assess the reliability of expert testimony in Vaccine Act cases). Petitioners' experts here described various aspects of immune function. They conceded that some factor, completely unknown to them, is needed to establish even a theoretical connection specifically between vaccination and herpes infection. Because the experts presented no reliable scientific evidence of what that unknown factor might be, their theory of possible vaccine causation was incomplete – petitioners did not show that the vaccine could have caused Doe's injury, thus failing to satisfy Prong 1.

Even if one were to accept Petitioners' medical theories as sufficient to satisfy Prong 1, Petitioners did not submit proof adequate to satisfy Prong 2 of a logical sequence of cause and effect between Doe's HSE and her vaccinations. Petitioners' evidence may be summarized as follows: HSE is rare, no one knows why Doe's herpes infection progressed to HSE, Doe received vaccinations shortly before her HSE manifested, therefore the vaccinations caused Doe's HSE. No evidence in Doe's medical's record supports the allegation of cause and effect between vaccine and injury. Petitioners did not identify any medical signs, symptoms, or conditions indicating that Doe's illness resulted from anything other than herpes infection. All the experts agreed that her illness followed the normal pattern for victims of HSE. All the

experts also agreed that no treating physician indicated a connection between Doe's HSE and her vaccinations.

In addition, Petitioners were unable to establish that the timing of events in Doe's case indicated vaccine injury. There is no reliable evidence concerning onset of the immune dysfunction that allegedly caused Doe's susceptibility to herpes, no reliable evidence of when Doe was exposed to the herpes virus, and no reliable evidence concerning timing of the alleged interaction between vaccination and herpes infection. Accordingly, Petitioners have not presented a prima facie case of entitlement and the Petition must be denied.

II. FACTUAL BACKGROUND

A. Medical Record

CHILD DOE/78 was born on July 26, 2005. Pet'r Ex. 4 at 31-33. She received a Hepatitis B vaccine on July 27, 2005. Id. at 19. She received the usual childhood vaccinations at nine months and one year. Pet'r Ex. 5 at 5-12. On May 2, 2007, at age 21 months, Doe was noted to be doing well, with normal development, and she received her third doses of Prevnar, Hib, and DTaP. Id. at 5, 9. Soon thereafter, Doe became ill while on an out-of-town visit, and she was admitted to Driscoll Children's Hospital ("DCH") after experiencing an illness for a couple of days followed by a sudden seizure. Pet'r Ex. 1 at 2. At her discharge, she was diagnosed with herpetic meningoencephalitis with secondary encephalomalacia, motor and language difficulties, and partial seizures. Pet'r Ex. 6 at 5.[2]

According to the history given by her parents, by May 8, 2007, Doe had developed a fever with decreased level of activity and fatigue. Id.[3] On the morning of May 10, 2010, Doe seemed relatively normal until she took a nap. Id. After the nap, she was drooling and unable to make eye contact, prompting her parents to call EMS. Id. Doe had a tonic clonic seizure in the ambulance on the way to the hospital. Id. Doe had another seizure in the DCH emergency room. Id. at 48. Cerebrospinal fluid ("CSF") obtained in the emergency room was abnormal and

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[2] Encephalomalacia: "the softening of the brain." Dorland's Illustrated Medical Dictionary 609 (30th ed.) [hereinafter "Dorland's"]. Meningoencephalitis: inflammation of the brain and membrane surrounding the brain and spinal cord. Dorland's at 1126.

[3] The DCH records vary somewhat concerning the onset and progress of Doe's illness. One history stated that at the time of admission, Doe had a two-day history of fever with decreased level of activity and fatigue. Pet. Ex. 6 at 5. Another stated that Doe had a low grade fever and some intermittent vomiting starting on May 7, 2007, that she was increasingly lethargic over the next few days, and on the morning of May 10, 2007, after a nap, lost normal eye contact, was weak and drooling, and suffered a generalized tonic-clonic seizure lasting about 10 minutes. Id. at 49; Pet'r Ex. 1 at 1-2. A third history reported that Doe was in her normal state of good health until the morning of May 8, 2007, when she was feverish and lethargic, and then she improved slightly on May 9, 2007. Pet'r Ex. 6 at 51. The Affidavit indicates that symptoms began on May 5, 2007. Pet'r Ex. 1.

indicated a viral infection. Id. Doe was hospitalized and treated with antibiotics and anti-seizure medications. Id.

On the morning of May 11, 2007, Doe had focal right-sided seizures. Id. at 42. A CT of the head was normal but an EEG was abnormal. Id. at 51-52. Doe was started on Acyclovir, an anti-viral drug, to treat a possible herpetic encephalitis. Id. She continued to be lethargic, but her fever abated after a couple of days. Id. at 6.

Over the next few weeks, doctors continued to try to isolate the cause of Doe's illness. A repeat CSF tap, taken on May 14, 2007, showed an elevated white blood cell count and was still negative for bacterial growth. Id. at 6. On May 14 and 15, her mental status was obtunded, her tone and posture flaccid, and she was assessed with meningoencephalitis, new onset seizures, and encephalopathy. Id. at 11, 13. Thereafter, she had no more seizures and her lethargy slowly improved. Id. at 7.

The polymerase chain reaction ("PCR") test on the May 17 CSF tap was positive for herpes simplex virus type 2 ("HSV-2"), consistent with the PCR results from the earlier May 10 CSF. Id. at 7.[4] It appears that no HSV PCR was run on the CSF sample from May 14, 2007. Other viral panels were negative. Id. at 32-34. Additionally, the sample was sent out for serology to identify any virus-specific antibodies. Id. at 36-41.[5]

On May 31, 2007, Doe was able to walk alone and use a few words. Id. at 7. An MRI performed on June 1, 2007, showed bilateral temporal lobe encephalomalacia. Id. at 7. Doe was discharged on June 2, 2007, and was noted to be alert, active, with some impulsive behavior and the use of many single words. Id. at 7-8.

After being discharged, Petitioners reported that Doe's condition deteriorated over the next few days. Pet'r Ex. 7 at 11. Five days later, on June 7, 2007, Doe was admitted to North Central Baptist Hospital, where she began her second prolonged stay in the hospital. Id. at 6, 11. The assessment was that her condition was consistent with a progressive encephalopathy, and she was admitted to the intensive care unit. Id. at 13-15. A CT of the brain, dated June 7, 2007, showed extensive damage. Id. at 352-53 (large areas of encephalomalacia and gliosis are seen with prominent volume loss). An MRI dated June 8, 2007, showed findings consistent with herpetic encephalitis. Id. at 328, 686. On July 6, 2007, Doe was transferred to Methodist

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[4] In most cases, an HSV "diagnosis can be established by PCR analysis of CSF. Large studies show PCR analysis to be 98 percent sensitive and 94 percent specific when compared with brain biopsy." Ann M. Martin, Herpes Simplex Viruses 1 and 2, Pediatric Infectious Diseases 1895 (5th Ed. 2004) (Resp't Ex. F.) (6% false positive and 2% false negative).

[5] Serology: refers to tests to "measure serum antibody titers in infectious disease (serological tests), to the clinical correlations of the antibody titer . . ., and to the use of serologic reactions to detect antigens . . ." Dorland's at 1685.

Children's Hospital for plasmapheresis and therapy, which improved her condition to a degree. Id. at 7; Pet'r Ex. 8 at 32-36.[6] The discharge summary stated the reason for admission as "post HSV encephalitis with chorea, for plasmapheresis." Pet'r Ex. 8 at 29. Doe received continued therapy at Warm Springs Rehab Hospital and, in January 2008, was noted to be making progress. Pet'r Ex. 9 at 4-5, 201-02.

According to the Petitioners' Post-Hearing Submission, Doe's disorder "has manifested as permanent neurological injuries including daily seizure events." Pet'r Post-Hr'g Submission, Mar. 8, 2010, at 2 [hereinafter "Pet'r Post-Hr'g Br."].

These facts are essentially undisputed. Also undisputed is the fact that the vaccines Doe received on May 2, 2007, were not the direct source of her herpes infection; that source is unknown. Tr. at 123, Oct. 1, 2009 (Dr. Kinsboune stated that he is "as much at a loss as anyone else in stating when exactly this infection took place").

Not all the facts are undisputed. Although the parties agree that Doe had HSE, they do not entirely agree as to which strain of the virus, HSV-1 or HSV-2, caused the encephalitis. Further, the parties do not entirely agree whether the infection was primary or recurrent. The main reason for the disagreements is inconsistencies in the results of the blood tests performed on Doe during her hospital stays.

The results of the serological studies done on Doe in May 2007 perplexed the experts for both parties. See, e.g., Tr. at 121-22. The tests did not detect the presence of HSV-2, which was shown to be in Doe's cerebrospinal fluid by PCR testing. See Tr. at 98 (Dr. Kennedy); Tr. at 181-82 (Dr. Klein). Given the PCR results, the antibody test results were the opposite of what the experts would have expected to see. Tr. at 99 (Dr. Kennedy); see Tr. at 130 (Dr. Kinsbourne). The experts entertained the possibility that there may have been contamination of the samples, or mistakes in the lab reports. Tr. at 99, 102. In his report, Dr. Kinsbourne stated that HSV-1 caused Doe's HSE, but at hearing, Dr. Kinsbourne assumed that the PCR results were reliable and stated that a recurrent HSV-2 infection caused Doe's HSE. See Tr. at 122. On the other hand, two of Respondent's experts felt this was a primary HSV-2 infection. Tr. at 55 (Dr. Leist); Tr. at 161-62 (Dr. Klein); Tr. at 193 (Dr. Herskowitz testified that he had nothing to add to the discussion by the experts in that area about HSV-1 versus HSV-2).

B. Herpetic Encephalitis

1. Herpes Simplex Virus

Herpes simplex viruses are widespread organisms that commonly infect humans. John H. Menkes, et al., Child Neurology, Ch. 7, 481 (7th Ed.) (Pet'r Ex. 68) [hereinafter "Menkes"];

[6] Plasmapheresis: "the removal of plasma from withdrawn blood, with retransfusion of the formed elements into the donor." Dorland's at 1446.

accord Nelson's Textbook of Pediatrics 1360 (Robert Kliegman, M.D., et al. eds., 18th ed. 2007) [hereinafter "Nelson's"]. They occur in two distinct serotypes: Type-1, which is generally associated with orofacial herpes infections, accounts for most cases of herpes simplex encephalitis in patients over six months of age, and Type-2, which is identified in genital herpes and accounts for most of the congenital or perinatally acquired infections. Menkes at 481; Tr. at 160-61. The locale of infection is not absolute, so HSV-1 can infect the genital tract, and HSV-2 can infect the upper respiratory tract. Id. at 161. Either Type-1 or Type-2 herpes can cause encephalitis, although Type-1 does so much more commonly after the post-neonatal period. Alexandros Kolokotronis & Stergios Doumas, Herpes Simplex Viral Infection, with Particular Reference to the Progression and Complications of Primary Herpetic Gingivostamatitis, Clinical Microbiology & Infection 12: 202-11, 208 (Mar. 2006) (Pet'r Ex. 16) [hereinafter "Kolokotronis"];[7] Tr. at 209-10 (post neonatal HSE is 80 percent Type 1, 20 percent Type 2); see Nelson's at 1363.

Herpes viruses are unique in "their neurotropism and their ability to remain latent in nerve and glial cells." Kolokotronis at 203.[8] The virus can remain in nerve collections in a latent, non-replicative state and remain there for the lifetime of the host. Dr. Kennedy's Expert Report at 9 (Pet'r Ex. 14) [hereinafter "Dr. Kennedy's Report"]. The virus has a known proclivity to reside in neural immune-privileged tissues, "and subsequently to elude the immune system 'reconnaissance,'" by means of well-understood biological properties. Kolokotronis at 203. From time to time, external events can stimulate the virus into an active state, which results in symptoms in the host, such as cold sores or fever blisters. Dr. Kennedy's Report at 9.

2. Herpes Simplex Encephalitis

The herpes simplex virus is the leading cause of sporadic encephalitis in the United States, and probably worldwide as well. Kolokotronis at 208; see also Dr. Kennedy's Report at 11. HSE "is an acute necrotizing infection generally involving the front and/or temporal cortex and the limbic system." Nelson's at 1363.[9] "The incidence of CNS [central nervous system] involvement in herpes simplex infections is uncertain," but "probably accounts for approximately 10% of all viral infections of the CNS." Menkes at 482.

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[7] This article was cited by and filed with Dr. Kinsbourne's expert report. Both the article and the report are filed as Exhibit 16.

[8] "Neurotropic" means "having a selective affinity for nervous tissue, or exerting its principal effect on the nervous system." Dorland's at 1260.

[9] "Necrotizing": causing necrosis, which is morphological changes from premature cell death. Dorland's at 1224-25. "Temporal cortex": this is the temporal lobe or lobus temporalis, which is the lower lateral lobe of the cerebral hemisphere of the brain. Id. at 1065. "Limbic system": a term loosely applied to a group of brain structures important for autonomic functions, certain aspects of emotion and behavior, and smell. Id. at 1843.

If untreated, herpes encephalitis "pursues an unremitting downhill course." Id. at 484. "The untreated infection progresses to coma and death in 75% of cases." Nelson's at 1363. Early therapy is advisable but "is not the only determinant" of outcome. Menkes at 484. Approximately one-half of young patients recover completely from the infection; however, some 5 to 26 percent of patients have relapses. Id. "The mortality from herpes simplex encephalitis is considerable, and approximately one-half of the survivors aged 5 to 11 years have major residual deficits" including disturbances in mental function, cognitive deficits, mental retardation, personality changes, lack of coordination, and seizures. Id. at 482; cf. Kolokotronis at 208 (stating that "mortality rates reach 60-70%," and "only 2.5% of surviving patients recover[] normal neurological function").

HSE can develop from a primary infection or from reactivation of a preexisting infection. Menkes at 481. Reactivation of a latent herpes virus "may sometimes occur spontaneously," but is "more often secondary to infection with human immunodeficiency virus, cancer, exposure to UV light, organ transplantation, pregnancy or menstruation, fever, cold, x-ray irradiation, chemotherapy, fractures, tooth extraction, sideropenia, gastrointestinal upset, surgery or other stress-inducing states." Kolokotronis at 205.[10]

The "gold standard" and test of choice for diagnosising HSE is polymerase chain reaction (PCR) testing to detect herpes DNA in the patient's cerebrospinal fluid. See Nelson's at 1364 ("Virus culture remains the gold standard for diagnosing HSV infections"); see also Menkes at 483 ("Rapid diagnosis of [HSE] can best be achieved by demonstration of viral DNA in the CSF by PCR[, and] [t]his [is now] the major diagnostic procedure").

Another method for detecting the virus is to use serological studies to test the blood for antibodies to HSV because "specific IgM and IgG responses occur in serum and CSF during the acute disease." Menkes at 482.[11] Serological assays generally are acknowledged to be less reliable than PCR testing for HSV. Nelson's at 1363-64 ("HSV immunoglobulin M (IgM) tests are notoriously unreliable, and the demonstration of a 4-fold or greater rise in HSV-specific IgG titers between acute and convalescent serum samples is only useful in retrospect"); see also Menkes at 483.

C. Petitioners' Theory of the Case

As summarized in their post-hearing submissions, Petitioners asserted that Doe would not have contracted HSE but for her vaccinations on May 2, 2007. They also submitted that the

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[10] "Sideropenia": iron deficiency. Dorland's at 1695.

[11] Ig stands for immunoglobulin, a group of structurally related glycoproteins that function as antibodies. Dorland's at 912. There are five classes of immunoglobulin, two of which are IgM and IgG. Id. "A rise in CSF or serum IgM herpes antibody correlates best with an active herpetic process." Menkes at 483.

vaccines exacerbated Doe's HSV infection, "with the ultimate result of viral encephalitis and the consequential, residual, neurologic damage." Pet'r Post-Hr'g Br. at 3. Relying on undisputed evidence that an infant's contraction of HSE is rare, Petitioners maintained that the cause for this unusual event was "the insult of the vaccines." Id. at 5. But for the vaccinations, they asserted, Doe would have had a typically mild reaction to the virus. Id. at 4. Petitioners contended that the vaccination weakened Doe's immune system to viruses, making her more vulnerable to HSV infection or reactivation. Id. at 8.

At hearing, Petitioners appeared to refine the theories of medical causation that were proposed in the submitted expert reports. These theories are described below. In sum, Petitioners appeared to make two claims: (1) that Doe contracted a primary HSV-2 infection that developed into encephalitis because of the vaccinations, and (2) Doe had a latent HSV-1 or HSV-2 infection or both that was reactivated by the vaccines. According to Dr. Kinsbourne, it is immaterial whether Doe's encephalitis was caused by HSV-1 or HSV-2 and whether the infection was primary or recurrent because Petitioners' theories would apply to any of those situations. However, Dr. Kinsbourne's opinion was that the medical record weighed in favor of Doe having a recurrent HSV-2 infection. Tr. at 129-33.

Petitioners relied on the Federal Circuit's decision in Shyface v. Secretary of Department of Health & Human Services, 165 F.3d 1344 (Fed. Cir. 1999), in which the Circuit "adopted the Restatement [of Torts] rule" that an action is the "'legal cause'" of harm if the action is a "'substantial factor'" in bringing about the harm and the harm would not have occurred "but for" the action. Petitioners asserted that, as recognized by the Restatement, concurrent forces may bring about a single harm. Pet'r Post-Hr'g Br. at 5-6. Petitioners stated that, in Shyface, "it was deemed impossible to know, with any degree of confidence, which source was the predominant cause" of the vaccinee's death. Id. at 6.[12]

I address the Shyface argument here to place in perspective the evidence and analysis of causation that follows in this decision. Shyface concerned an infant who was vaccinated with the DPT vaccine, fell ill several days later, and died from pneumonia, with a fever of 109 degrees. 165 F.3d at 1345-46. Petitioner's expert in Shyface testified that, although the child also suffered from an E. coli infection, but for the vaccination the child would not have died. "[I]t was the combination of the two [identified causes] that caused his death." Id. at 1346. The special master credited the petitioners' expert testimony that the child's temperature was "'much

[12] Some confusion is evident in Petitioners' presentation of this aspect of their case. Petitioners assert in their Post-Hearing Brief that this situation is "[a]nalogous" to Shyface because "it is impossible to know with any degree of confidence whether petitioner had primary HSV or a reactivation of HSV, and whether she had HSV-1, HSV-2 or both." Pet'r Post-Hr'g Br. at 6 (emphasis in original). Deciding which type of herpes infection Doe suffered is not the significant issue, however. For Shyface to apply, it would be necessary to show that both the herpes infection and one or more vaccines more likely than not caused the encephalitis. Petitioners, as discussed herein, have not shown that the vaccinations either caused or contributed to Doe's injury.

higher than would be expected in the case of an E. coli infection alone, particularly at the moderate levels of infection indicated by test cultures.'" Id.

The special master initially ruled for the petitioners, but after conducting further proceedings on remand from the reviewing judge, found that there was no preponderant evidence showing that vaccination caused the vaccinee's death. Id. at 1347. The Court of Federal Claims then sustained the denial of compensation, but the Federal Circuit reversed, stating that petitioners were not required to show that vaccination was a preponderant cause of the vaccinee's death, so long as they could prove that it was a "but for" and "substantial cause." The Circuit expressly relied on the special master's findings that (1) the vaccinee would not have died but for the DPT vaccination; (2) the DPT vaccination contributed to the vaccinee's death by causing "an exceptionally high fever," and (3) sepsis, due to E-coli infection, was not the only or predominant cause of the vaccinee's death. Id. at 1353.

Simply arguing that vaccination contributed to the injury does not bring a petitioner within the ambit of the Shyface doctrine. Petitioners still must present sufficient evidence to support "but for" and "substantial" causation. I do not see such evidence in this case. The first theory presented by Dr. Kennedy, involving a "cascade of events" triggered by vaccination-induced cytokine response, is not supported by reliable evidence and does not explain what happened in this case, in any event, as discussed below in the analysis of Althen Prong 1. Dr. Kinsbourne, the second Petitioners' expert, at hearing changed his theory of causation from a pro-inflammatory cytokine cascade to Th-skewing, the theory that Doe was pre-disposed by her bacterial vaccinations to suffer unduly from herpes infection. That theory also is unsupported by reliable evidence and equally incapable of establishing a logical sequence of cause and effect explaining what happened in this case, as discussed infra. Thus, as a factual matter, Petitioners have not presented evidence that would result in an award under a Shyface theory.

There is no reliable evidence before me, considering the record as a whole, that establishes that vaccines caused or even contributed to Doe's injuries. Petitioners' experts barely addressed the issue of whether the vaccines could or did cause encephalitis in this case – in other words, whether they were a "but for" cause. Petitioners' experts focused instead on how vaccination could have led to HSE, which they conceded was the cause of Doe's catastrophic brain injury. Indeed, Petitioners' experts agreed that the course of Doe's disease was typical of someone who, for whatever reason, contracts HSE. This is in vivid contradistinction to the facts found in Shyface, where there was preponderant evidence that the vaccinee's fatal fever would not have been as severe absent his DPT vaccination.

D. Respondent's Theory of the Case

Respondent has claimed that Petitioners did not carry their burden of establishing a prima

facie case of actual causation.[13] With respect to Prong 1, Respondent asserted that Petitioners' "explanation as to how the vaccines 'can cause' the injuries alleged is based on guesswork and speculation." Resp't Post-Hr'g Br. at 6. Respondent maintained that Petitioners' theory is unreliable for three reasons. First, "none of [Doe's] treating physicians support vaccine causation for her herpes encephalitis." Id. at 8. Second, Respondent asserted, as a factual matter, that Doe most likely suffered from a primary HSV-2 infection, and "her injury was solely explained by the effects of this infection." Id. at 9-10. Finally, Respondent maintained that Petitioners' experts undermined their theory of causation during their testimony at hearing. Id. at 13.

With respect to Prong 2, Respondent asserted that the logical sequence of cause and effect proffered by Petitioners was not sufficiently reliable. Id. at 14. Respondent contended that "the logical conclusion from the evidence is that [Doe's] encephalitis stemmed from a primary HSV-2 infection, which was coincidental to her vaccination but had absolutely no connection to it." Id. at 14. Doe "had all of the classic signs and symptoms of herpes encephalitis," and HSV-2 virus was present in Doe's CSF. Id. at 15. Further, she had no medical history that is consistent with the theory that her illness was caused by a reactivation or recurrence of a latent herpes infection (disputing Dr. Kinsbourne's theory).[14] Respondent concluded that a primary HSV-2 infection caused Doe's encephalitis, and that Petitioners have presented insufficient evidence to show that the vaccines caused or contributed to the HSE.

III. DISCUSSION

A. Petitioners' Burden of Proof to Demonstrate Causation-In-Fact

The Vaccine Act created the National Vaccine Injury Compensation Program ("Vaccine Program") under which compensation may be paid for vaccine-related injury or death. 42 U.S.C. § 300aa-10(a); Walther v. Sec'y of Dep't of Health & Human Servs., 485 F.3d 1146, 1149 (Fed. Cir. 2007). Pursuant to the Vaccine Act, petitioners may be compensated for injuries caused by certain vaccines. See generally §§ 300aa-10 to 34. To receive compensation, a petitioner must

[13] Respondent asserts that Petitioners also allege a significant aggravation theory. I question whether that is an accurate characterization of the Petitioners' arguments, in light of Petitioners' assertion that Doe was a perfectly well child before her vaccinations on May 2, 2007. See Pet'r Post-Hr'g Br. at 1. In any event, the evidence fails to show the requisite causal connection between vaccination and susceptibility to herpes infection or reactivation, as discussed below, whether the theory is straightforward causation or significant aggravation. See Loving v. Sec'y of Dep't of Health & Human Servs., 86 Fed. Cl. 135, 144 (2009).

[14] In a footnote, the Secretary asserted that Petitioners failed to satisfy Althen Prong 3 because "none of petitioners' experts . . . gave reliable testimony on a medically-appropriate time period for vaccine causation.'" Resp't Post-Hr'g Br. at 5, n.5. The Secretary asserted that Doe's onset of illness was outside the time period where the vaccines may have had an indirect effect on her herpes encephalitis. Id.

prove that either: 1) he suffered a "Table Injury"– that is, an injury falling within the Vaccine Injury Table – corresponding to one of his vaccinations, or 2) he suffered an "off-Table" injury that was actually caused by or "caused-in-fact" by a vaccine. See §§ 300aa-13(a)(1)(A), 300aa-11(c)(1); Shalala v. Whitecotton, 514 U.S. 268, 270 (1995). In this case, Petitioners have alleged that Doe suffered an off-Table injury.

To satisfy their burden of proving causation in fact, Petitioners must show not only that but for Doe's vaccinations she would not have been injured, but also that the vaccinations were a substantial factor in bringing about her injury. Shyface,165 F.3d at 1352. Mere temporal association is not sufficient to prove causation in fact; a petitioner must present a medical theory grounded either in facts in the medical record or in the opinion of a competent physician. Grant v. Sec'y of Dep't of Health & Human Servs., 956 F.2d 1144, 1148 (Fed. Cir. 1992). Proof of actual causation must be based on a sound and reliable "medical or scientific explanation that pertains specifically to the petitioner's case, although the explanation need only be 'legally probable, not medically or scientifically certain.'" Moberly v. Sec'y of Dep't of Health & Human Servs., 592 F.3d 1315, 1322 (Fed. Cir. 2010) (quoting Knudsen v. Sec'y of Dep't of Health & Human Servs., 35 F.3d 543, 548-49 (Fed. Cir. 1994)) (emphasis added); accord Grant, 956 F.2d at 1148.

The preponderance of evidence standard under the Vaccine Act requires proof that a vaccine more likely than not caused the vaccinee's injury. Althen, 418 F.3d at 1279. Causation is determined on a case by case basis, with "no hard and fast per se scientific or medical rules." Knudsen, 35 F.3d at 548. A petitioner may use circumstantial evidence to prove her case, and "close calls" regarding causation must be resolved in favor of the petitioner. Althen, 418 F.3d at 1280.

Once the petitioner has met the initial burden of proof, "the burden shifts to the government to prove by a preponderance of the evidence that the petitioner's injury is due to factors unrelated to the . . . vaccine. . . ." de Bazan v. Sec'y of Dep't of Health & Human Servs., 539 F.3d 1347, 1352 (Fed. Cir. 2008) (quotations omitted). If the petitioner fails to establish a prima facie case of causation, however, the burden does not shift to respondent. Doe 11 v. Sec'y of Dep't of Health & Human Servs., 601 F.3d 1359, 1357-58 (Fed. Cir. 2010). To decide whether a petitioner has established a prima facie case, the special master may consider all of the evidence presented, including evidence of alternative causes if it bears directly upon the sufficiency of the petitioner's evidence. Doe 11, 601 F.3d at 1357 (holding that when the petitioner tried to rule out an alternative cause of death, the special master could consider whether the petitioner actually ruled out the alternative); de Bazan, 539 F.3d at 1353-54 (holding that the special master could consider evidence showing that onset timing was inconsistent with vaccine causation but consistent with alternative causation).

In determining whether a petitioner has presented a legally probable medical theory, "the special master is entitled to require some indicia of reliability to support the assertion of the expert witness." Moberly, 592 F.3d at 1324. Assessing the reliability of expert in opinion in

Vaccine Act cases can be challenging because often there is little confirmatory evidence for the expert's opinion. See Althen, 418 F.3d at 1280 (noting that the "field [is] bereft of complete and direct proof of how vaccines affect the human body"). Reliable expert opinion is based on scientific data and inferences reasonably to be drawn from the facts. See Daubert, 509 U.S. at 590 (defining scientific knowledge as "'any body of known facts or [] any body of ideas inferred from such facts or accepted as truths on good grounds'") (citation omitted). Evaluation of the reliability of an expert's opinion thus depends in part on the size of the gap between the scientific data and the opinion proffered. See Snyder v. Sec'y of Dep't of Health & Human Servs., 88 Fed. Cl. 706, 745 (2009) (finding no error in the special master's application of the Daubert framework to assess the weight to be given to expert testimony).

B. Could Vaccination Have Caused Doe's Injuries? – Prong 1

Under Althen Prong 1, a petitioner must set forth a biologically plausible theory explaining how the vaccine received by the petitioner could cause the injury complained of. See, e.g., Andreu v. Sec'y of Dep't of Health & Human Servs., 569 F.3d 1367, 1375 (Fed. Cir. 2009). This requirement has been interpreted as "can the vaccine(s) at issue cause the type of injury alleged?" Pafford, 451 F.3d 1352, 1355-56 (Fed. Cir. 2006). Evidence should be viewed by the preponderance of the evidence standard and "not through the lens of the laboratorian." Andreu, 569 F.3d at 1380. Although the theory of causation need not be corroborated by medical literature or epidemiological evidence, the theory must be sound, reliable, and reputable—in other words, the theory need not be scientifically certain, but it must have a scientific basis. See Andreu, 569 F.3d at 1379-80.

In accordance with the authorities cited above, a special master need not rely on a speculative opinion that "'is connected to existing data only by the ipse dixit of the expert.'" Snyder, 88 Fed. Cl. at 745, n.66 (quoting Gen. Elec. Co. v. Joiner, 522 U.S. 136, 147 (1997)). Under Prong 1, the question is not whether vaccine injury is possible under any imaginable set of circumstances, but whether is it possible based on facts known to medical science and logical inferences drawn from the facts by a qualified expert.

In this case, Petitioners presented two theories from Dr. Kennedy to satisfy their burden under Prong 1. The submitted evidence shows that Petitioners have not expounded a reliable theory that vaccines could have caused Doe's injury.

1. Dr. Ronald Kennedy's Opinion[15]

Dr. Ronald Kennedy is a Ph.D. immunologist with extensive research experience in the areas of viruses and vaccines. Tr. at 5-11. He is not a medical doctor and his research has focused mainly on primates other than humans. Id. at 13-14. He has published some 254

[15] Dr. Kinsbourne's testimony is described in the analysis of Prong 2 below. At hearing, he simply adopted Dr. Kennedy's theory of general causation. See Tr. at 147.

articles, of which 10 or 11 relate to the herpes simplex virus, the last of those dealing with humans published in 1985. Id. at 13. Dr. Kennedy was extrapolating from his research in non-human immune systems when he gave his opinion regarding the possible causation of Doe's illness.

In his expert report (Pet'r Ex. 14), Dr. Kennedy stated, "my opinion [is] that individual and/or a combination of the vaccine components and subsequent activation of an innate immune response resulted in the production of specific inflammatory factors, term [sic] cytokines[,] that were substantial factors in the exacerbation of the herpes simplex infection and the resulting encephalitis in [Doe]," and it is based in part on "my expertise in the area of Viral Immunology and Vaccine related basic research activities." Dr. Kennedy's Report at 1. He outlined the key elements of his opinion, stating:

> * Components within the pediatric vaccine regimen can activate the innate immune system, resulting in an inflammatory response.
>
> *[Activation of] the innate immune system, [causes cells to] secrete inflammatory factors and mediators, referred to as cytokines.
>
> * Selected cytokines have been associated with exacerbation of primary [HSV] infection and associated with reactivation of a latent [HSV] infection.
>
> * Exacerbation of either primary [HSV] infection or reactivation of a latent [HSV] infection set [sic] up a cascade of events that lead to encephalitis rather than an asymptomatic or localized infection . . .
>
> * There are a number of adverse reactions individually listed for DTaP, Hib, and Prevnar vaccines that are . . . hallmark signs of inflammation that involve local and systemic effects.
>
> * A primary [HSV] infection or reactivation of a latent [HSV] infection following the booster combination pediatric vaccinations provided to [Doe] resulted in [HSV] encephalitis.

Dr. Kennedy's Report at 1-2.

Dr. Kennedy explained his theory in his report. He described the inflammatory reaction that takes place at the cellular level as part of the immune system's response to a foreign substance. Id. at 6-8. Once a white blood cell detects a foreign substance via receptors on the cell's surface, it secretes chemicals called cytokines. Id. There are a variety of different types of cytokines, and each particular cytokine stimulates the immune system to take a particular action against the invading substance (or takes the action itself). Id. The immune system has an innate reaction to foreign substances and an adaptive, or learned, reaction. Id. The innate reaction

ordinarily will involve the secretion of specific cytokines to recruit more cells to the affected area and cause inflammation. Id. The adaptive reaction occurs if a white blood cell recognizes the foreign substance, and then the cell will secrete cytokines to make the immune system take the actions that worked against the substance the last time it was encountered. Id.

Dr. Kennedy described the characteristics of herpes virus infections, noting the ability of the virus to remain in the body in a latent state for long periods after initial infection, subject to reactivation as a result of "provocative stimuli," including "axonal injury, fever, physical, psychological or emotional stress, like inflammation or a death in the family, and exposure of ultraviolet light." Id. at 9-10. He explained that, "either a primary or recurrent infection by HSV can result in active viral replication that manifests as a particular symptom or disease, like fever blisters or encephalitis." Id. at 10. HSV infections, both primary and recurrent, are the most common cause of sporadic, fatal encephalitis. Id. at 11.

"Selected proinflammatory cytokines," Dr. Kennedy stated, "have been associated with exacerbation of a primary herpes simplex virus infection and associated with reactivation of a latent herpes simplex virus infection." Id. at 15. The literature concerning HSV that Dr. Kennedy cited, which mostly discussed results of experiments performed on mice, shows that some cytokines appear to suppress reactivation of HSV, see, e.g., Pet'r Exs. 31-34, 36, 38, while others appear to stimulate reactivation, see, e.g., Pet'r Exs. 25, 27, 38. The literature explains that cytokines can be divided into two groups, T helper 1 ("Th1") cytokines, which stimulate an immune response that typically targets viruses, and Th2 cytokines, which stimulate an immune response that typically enhances protection against bacteria. Tr. 15-16; see also Pet'r Ex. 49; Pet'r Ex. 53. Certain Th1 cytokines suppress production of Th2 cytokines, and certain Th2 cytokines suppress production of Th1 cytokines. Pet'r Ex. 53. Dr. Kennedy stated that the immune system's innate response to vaccines can release proinflammatory cytokines, which block production of Th1 cytokines and also have been associated with stimulating HSV reactivation, thereby reducing protection against viruses and allowing HSV reactivation to occur. Dr. Kennedy's Report at 10. This is what happened to Doe, he opined. Id. at 11.

Dr. Kennedy discussed a number of the DTP and DTaP vaccines' known side effects, which he claimed are "hallmark signs of inflammation and the activation of the innate immune system." Id. at 12.[16] Dr. Kennedy also discussed adverse side effects noted from administration of the Hib and Prevnar vaccines, which included reactions such as local and systemic

[16] In discussing adverse events allegedly associated with the whole cell pertussis vaccines ("DTP"), which Dr. Kennedy testified also arise following administration of the acellular vaccine, Dr. Kennedy cited the work of the Geiers. David A. Geier & Mark R. Geier, An Evaluation of Serious Neurological Disorders Following Immunization: A Comparison of Whole-Cell Pertussis and Acellular Pertussis Vaccines, Brain & Dev. 26(2004) 296-300 (Pet'r Ex. 28). For persuasive reasons, which I adopt, the Geiers' work has been found unreliable in other cases. See, e.g., Snyder v. Sec'y of Dep't of Health & Human Servs., No. 01-162V, 2009 WL 332044, *69, n.204 (Fed. Cl. Spec. Mstr. Feb. 12, 2009).

inflammation, fever, drowsiness, vomiting, and diarrhea. Id. at 13-14. Dr. Kennedy stated that some studies have demonstrated that the DTaP vaccine can polarize the immune system's cytokine response, and that this polarization is associated with local reaction at the injection site. Id. at 14.

Dr. Kennedy concluded that certain pediatric vaccines "are comprised of bacterial components that are capable of . . . activating cytokine production and inflammation." Id. at 14. He asserted that the cytokines associated with inflammation are the same ones associated with HSV reactivation, and that Doe manifested "local and systemic effects that are hallmarks of inflammation" occurring in children after vaccination. Id. at 14-15. Therefore, it was Dr. Kennedy's opinion that Doe's HSV infection or reactivation was provoked by the inflammation and cytokine reactions that were caused by her vaccinations. Id. In a supplemental expert report, Dr. Kennedy submitted several VAERS reports and a case report in "The Lancet" documenting HSV reactivation following vaccination. Dr. Kennedy's Supplemental Report (Pet'r Ex. 58).

At hearing, Dr. Kennedy described a second causation theory. He testified that the "mechanism" of vaccine causation in Doe's case was that her receipt of "bacterial vaccines . . . pre-programmed" her immune system "to enhance the protective activities against bacteria at the detriment of those protective vaccines against infectious agents such as viruses, and this includes herpes simplex virus, HSV." Tr. at 15-16. In other words, the early receipt of bacterial vaccines skewed Doe's immune system to release, in response to the DTaP vaccine, more Th2 cytokines thereby suppressing the level of Th1 cytokines. According to Dr. Kennedy, the decrease in the Th1 cytokine level "resulted in an exacerbation of the infection and disease, and a serious manifestation of which is the encephalitis." Id. at 16.[17]

Under both Dr. Kennedy's theories, it is unimportant whether the infection was primary or recurrent, or whether the type of virus was HSV-1 or HSV-2, because the vaccine weakened Doe's immune response to viruses generally. Id. at 16-17. Dr. Kennedy relied on two articles that he said examined the ability of DTaP vaccine to "preprogram or skew the immune response," such that it protects against bacterial infection but not against certain viruses "such as herpes simplex." Tr. at 27-28, 36-41.[18]

On cross-examination, Dr. Kennedy agreed that none of Doe's treating physicians attributed her herpes encephalitis to the vaccines. Tr. at 18. He stated that any one of the

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[17] A similar theory was advanced and rejected in Snyder to show that the MMR vaccine suppressed the immune system's response to viruses. See Snyder, 2009 WL 332044, at *57, *98.

[18] J. Macaubas Rowe, et al., Antigen Specific Responses to Diphtheria-Tetanus-Acellular Pertussis Vaccine in Human Infants Are Initially Th2 Polarized, Infection and Immunity 68:3873-77 (2000) (Pet'r Ex. 49); J. Rowe, et al., Th2 Associated Local Reactions to the Acellular Diphtheria-Teatanus-Pertussis Vaccine in 4 to 6 Year Old Children, Infection and Immunity 73:8130-35 (2005) (Pet'r Ex. 50); see also O.J. White et al., Th-2 Polarization of Cellular Immune Memory to Neonatal Pertussis Vaccination, Vaccine 28: 2648-52 (2010) (Pet'r Ex. 64).

vaccines Doe received on May 2, 2007, or any combination of them, could have been causative. Id. at 18. He also stated that, in Doe's medical history, there was "[n]o evidence of recurrent bacterial or viral infections." Id. at 20. He agreed that Doe's records were devoid of any mention of an inflammatory reaction at the vaccine site. Id. at 26. Dr. Kennedy agreed that most of the articles concerning herpes that he referred to in his reports discussed reactivation rather than primary herpes infection. Id. at 25-26, 29.

Regarding the question whether Doe's herpes infection was primary or latent, Dr. Kennedy felt it was a latent infection based on the serology, but he stated that the only evidence of a latent infection was the serology and "again I feel the serology was incomplete based on the medical records." Id. at 35.

As Dr. Kennedy described his "skewing" theory, it would only result in weakness to viruses in some individuals, not all, depending on their individual immune response. Tr. at 39-42. To show that the immune system can be impaired by vaccines, Dr. Kennedy referred to his supplemental report, where he identified several VAERS reports and a case report in "The Lancet." Tr. at 43; Dr. Kennedy's Supplemental Report at 1. Nonetheless, he agreed that if his theory applied to the general population, the literature would show a great many more reports of such vaccine injury than the few he was able to identify. Tr. at 43-44 ("So at an epidemiological level, it has not gone to the point of being a general major concern"). Asked whether he had "a theory as to why Doe's immune system reacted in the way [he] described," Dr. Kennedy responded, "no, but it would be an interesting individual to look at." Id. at 42-43. Neither Dr. Kennedy nor any other expert testified that Doe had a genetic abnormality. See, e.g., Tr. at 105-06; Id. at 120.

2. Dr. Thomas Leist's Opinion

Dr. Thomas Leist is a practicing adult neurologist who has conducted research in neuroimmunology. Tr. at 48-52; Resp't Ex. K (Dr. Leist's CV). Although Dr. Leist admitted that Dr. Kennedy's theories were possible, he stated that Dr. Kennedy's chain of logic was attenuated and incomplete. Tr. at 87-89 (noting that Dr. Kennedy's individual arguments are not tied together); Tr. at 64-65 (challenging whether the literature cited by Dr. Kennedy actually supported the Th2 skewing mechanism); Dr. Leist's Expert Report at 10-12 (Resp't Ex. J) [hereinafter "Dr. Leist's Report"] (citing literature showing that for a specific chemical, clinical human trials met with different results than did murine models). "In anything that we do, cytokines are induced." Id. at 86. "Along the axis of our life, we are continuously exposed to bacterial and fungal . . . pathogens, all of which tend to switch to a Th2 response." Id. at 89. Dr. Leist saw no evidence that could explain why an immune process that occurs frequently in both vaccinated and unvaccinated persons would cause a weakening of Doe's immune system only in one instance. Id. at 86-89.

3. Dr. Jerome Klein's Opinion

For more than 50 years, Dr. Jerome Klein has been a practicing pediatrician specializing in infectious diseases, on which he has conducted extensive research. Tr. at 156 -57. Dr. Klein has "never seen or heard of a case of HSV encephalitis causally related to a vaccine. . . ." Dr. Klein's Expert Report at 4 of 5 (Resp't Ex. D) [hereinafter "Dr. Klein's Report"]. Due to the millions of routine juvenile immunizations, he stated that "by chance alone there would be a temporal association of a recent immunization with the HSV encephalitis in an infant." Id. Dr. Klein testified that he had served on a Centers for Disease Control ("CDC") committee that examined VAERS reports, and that although a few reports of temporal association between HSE and vaccines have been made, the evidence did not substantiate a causal connection between HSE and vaccines. Tr. at 167-69, 179-80.

At hearing, Dr. Klein criticized Dr. Kennedy's report as a "theory of possibilities." Id. at 166. He discounted the probative value of the articles that were cited by Dr. Kennedy and stated that there is no reliable medical literature that can bridge the gap between Dr. Kennedy's theory and what is known about immune response. Tr. at 167-69. Dr. Klein testified that because immunizations have a central role "in our fabric of preventative medicine. . .[,] anything that is possible should be investigated, but" the theory that Doe's vaccinations caused her HSE is "beyond the realm of even biologically plausible or possible." Id. at 174-75.

4. Dr. Joel Herskowitz's Opinion

Dr. Joel Herskowitz is a pediatric neurologist. See Resp't Ex. B (CV). In his expert report, he stated that Dr. Kennedy had presented a "plausible hypothesis" that was a "possible" but not a "probable" theory of causation. Dr. Herskowitz's Expert Report at 6 (Resp't Ex. A) [hereinafter "Dr. Herskowitz's Report"]; see Tr. at 197. Dr. Herskowitz stated that he looked for reasons to find in favor of Petitioners, but he could not find a compelling link other than coincidence. Tr. at 190. Throughout his testimony, he gave examples of the type of evidence that could provide such a link in this case: medical literature, a compelling history in Doe's clinical sequence, a documented increase in reports of illness 3-10 days following vaccination, or anecdotal evidence or a gut feeling from experienced clinicians. Tr. at 190-91, 195, 203-204.

Dr. Herskowitz stated that he could find no evidence to indicate that this was anything more than a case of HSE. He did not find any medical literature that substantiated Petitioners' theories. Tr. at 190-92. He agreed with Dr. Klein that Doe's symptoms were consistent with HSE. Dr. Herskowitz's Report at 7; see Tr. at 192 ("Take away the set of immunizations, and the clinical course is fully consistent with herpes encephalitis"). Although millions of children have received millions of vaccines, there is not enough evidence, in either the medical literature or anecdotal clinician experience, even to raise a concern about vaccines causing a temporary immune deficiency. Tr. at 195. In sum, Dr. Herskowitz thought that Dr. Kennedy proposed "an interesting hypothesis[,] but the next step is simply not there." Tr. at 194.

5. Analysis of Prong 1

In part, Dr. Kennedy's opinions are based on application of animal laboratory studies to humans. To fill in the gaps between the scientific literature and his ultimate opinion, Dr. Kennedy engaged in a certain amount of speculation. Although every step of Dr. Kennedy's reasoning need not be confirmed by scientific literature, a theory of possible vaccine causation must have a scientific basis. "[A]n expert opinion is no better than the soundness of the reasons supporting it." Perreira v. Sec'y of Dep't of Health & Human Servs., 33 F.3d 1375, 1377 n.6 (Fed. Cir. 1994); see Snyder, 88 Fed. Cl. at 745, n.66 (quoting Daubert, 509 U.S. at 579).

Respondent's experts took issue with Dr. Kennedy's conclusions. Dr. Klein testified that Dr. Kennedy's theory is inconsistent with what is known about vaccines and inflammation, and the gaps between the cited literature and Dr. Kennedy's theories were too large for his theories to be reliable. Tr. at 167-69, 185. Dr. Joel Herskowitz, one of Respondent's experts, stated that Dr. Kennedy had presented a "plausible" theory, see Tr. at 202, but he was not persuaded, without confirming evidence in medical literature or a "compelling story" in the clinical sequence, that the theory was operative in Doe's case. Tr. at 191-94.

I agree with the Secretary's experts that, to connect the literature to a conclusion of vaccine causation in this case, Dr. Kennedy must fill some large gaps in the evidence. Two gaps merit special note. First, none of the articles cited by Dr. Kennedy establishes a causal relationship between a cytokine and HSV reactivation in humans. The literature noted that the possible association in murine models was merely suggestive for human systems. See, e.g., John D. Kriesel et al., Neuronal Reactivation of Herpes Simplex Virus May Involve Interleukin-6, J. Neurovirology 3(6):441-48 (Dec. 1997) (Pet'r Ex. 32) (stating that based on the results of the murine experiment, "exploring the role of IL-6[, an inflammatory cytokine,] in HSV-1 reactivation is a promising new avenue of research into the mechanism of HSV reactivation"); John D. Kriesel et al., Signal Transducers and Activators of Transcription (Stat) Are Detectable in Mouse Trigeminal Ganglion Neurons, J. Interferon and Cytokine Research 21:445-50, 449 (2001) (Pet'r Ex. 34) ("this [murine] study supports the feasibility of the cytokine-Stat hypothesis of HSV-1 reactivation. . . . Further studies are planned to explore the profile of Stat and activation status in [the] human [nervous system]"). Although animal studies are relevant, their results should be relied upon with caution. Tr. at 175 (Dr. Klein); Dr. Leist's Report at 12 (noting that an agent that reduced HSV infections in animals had no clinical effect in humans).[19]

Second, neither the literature nor clinical experience indicates that inflammatory cytokine reactions or "Th-skewing" compromises a person's immune system. Every person is continually exposed to environmental pathogens, and the immune system is continually reacting with

[19] Animal studies have limitations because the effects of a drug may differ in animals and humans. For example, saccharin causes cancer in rodents, but not in humans. Tylenol, even in extremely small doses, is lethal to cats. See, e.g., Goewey v. U.S., 886 F.Supp. 1268 (D.S.C. 1995) (neurotoxic effects of substance in chickens cannot be extrapolated to humans, absent some epidemiologic confirmation). See also Gen. Elec., 522 U.S. at 144-45 (district court did not abuse its discretion in excluding animal studies that did not involve the same modes of exposure as in humans).

cytokines. Tr. at 65. Beyond the very general assertion that each individual's immune system is unique, Dr. Kennedy could provide no plausible theory explaining how Doe's natural responses to a foreign substance in the vaccines could have resulted in greater susceptibility to herpes virus. Dr. Kennedy did provide several isolated examples of post-vaccine herpes reactivation in humans. See Pet'r Exs. 58, 59. Given the far-reaching implications of his theories, however, he agreed that such incidents should be numerous, not sporadic, if in fact there was a possible connection between vaccination and herpes. Recognizing the insufficiency of his explanations, Dr. Kennedy testified that something in addition to vaccination must have caused Doe's reaction. Dr. Kennedy had "no idea at all" what that something might be. Tr. at 43.

Dr. Kennedy's theories are supported by scientific evidence, but they are too general to support possible causation in this case. Cytokine release is a well-recognized aspect of immune function; thus the phenomenon posited by Dr. Kennedy as a possible cause of Doe's HSE would affect enormous numbers of vaccinees. Similarly, his "Th-skewing" theory would affect every individual who receives a bacterial vaccine. In fact, Dr. Kennedy's theories apply to any of the three vaccines Doe received on May 2, 2007. See Tr. at 126 (according to Dr. Kinsbourne "by the logic of it[,] . . . [Dr. Kennedy's theory would] really appl[y] to any bacterial vaccine"). The theories do not postulate a biological link between vaccination and immune dysfunction that could result specifically in HSE. While epidemiological studies are not required to satisfy Prong 1, the absence of evidence explaining in the specific instance an effect which, as described by Dr. Kennedy, would be nearly universal, detracts from the persuasiveness of his theory. Again, the record reflects a few, isolated reports of HSV infections occurring post-vaccination, see Dr. Kennedy's Supplemental Report, but the reports, according to the evidence from the Secretary's experts in immunology, have not raised the possibility in the medical community of an association between vaccination and herpes, Tr. at 169, 174 (Dr. Klein); Tr. at 203-04 (Dr. Herskowitz).[20]

In addition, Doe's medical record provides no support for Dr. Kennedy's theories. As stated by Dr. Herskowitz, a "compelling story" in the clinical sequence could make up for the lack of confirmatory scientific evidence. See Knudsen, 35 F.3d at 548 (causation can be found based on "epidemiological evidence and the clinical picture regarding the particular child"). The medical record here, on the contrary, shows that Doe's condition, though rare, was fully consistent with a typical case of HSE. Doe's clinical course did not suggest that some other immunological mechanism was at work. No treating professional indicated even a suspicion that Doe's HSE was linked to vaccination. Thus, nothing in the record fills in the blank left by Dr. Kennedy's theory, namely, how Doe's immune system could have been compromised by vaccinations in a way that caused her to contract HSE. In sum, Petitioners did not present a reliable medical or scientific theory of possible vaccine causation that pertains specifically to this

[20] The analysis would be different if Petitioner could point to any plausible link between the vaccinations received and HSE. See, e.g., Rotoli v. Sec'y of Dep't of Health & Human Servs., 89 Fed. Cl. 71, 83 (2009) (link between wild hepatitis virus and autoimmune hepatitis supports a finding that hepatitis B vaccine can cause autoimmune hepatitis).

case. See Moberly, 592 F.3d at 1322.

Petitioners' theories are not supported by facts or inferences therefrom sufficient to forge the link between the general hypothesis that vaccines weaken the immune system and Doe's condition. The problem is that the theories are incomplete, not that they are unproven. See Rotoli, 89 Fed. Cl. at 79 (noting the "fact that a link between a vaccine and a particular injury is a 'sequence hitherto unproven in medicine' will not bar recovery") (citations omitted).[21] The proposition that vaccines in general compromise the immune system in a way that left Doe vulnerable to herpes infection has not been shown by reliable experimentation, epidemiology, or expert opinion, and as expressed by the Secretary's experts in this case, is not based on logic or scientific knowledge. On the contrary, critical testimony for the petitioner consists of pure speculation. See Tr. at 134 (Dr. Kinsbourne stating that "with something like this you must think of a multidimensional convergence [of factors], but clearly we can't precisely stipulate what it was"). In his report, Dr. Kennedy stated that Doe's vaccinations "set up a cascade of events that [led] to encephalitis rather than an asymptomatic or localized infection"; however, he provided no factual information concerning what those events were or any indication that they actually occurred in this case. Dr. Kennedy's Report at 1. When asked whether he had "any theory as to what it was about [Doe's] immune system that made her vulnerable to the vaccine she received in the way that [he had] described," Dr. Kennedy replied "I have no idea at all." Tr. at 42-43.

As noted above, "causation can be found . . . without detailed medical and scientific exposition on the biological mechanisms." Knudsen, 35 F.3d at 549. Causation can be found based on reliable medical testimony alone. See Althen, 418 F.3d at 1278. Causation cannot be found, however, based on "no idea at all." On the record before me there is no reliable medical testimony that the vaccinations Doe received can cause or exacerbate HSE, and therefore no basis on which to find for Petitioners under Althen Prong I.

C. Evidence of a Logical Sequence of Cause and Effect – Prong 2

The second prong of Althen requires a petitioner to prove "'a logical sequence of cause and effect show[ing] that the vaccination was the reason for the injury.'" Andreu, 569 F.3d at 1374 (quoting Althen). Under Prong 2 of Althen, Petitioners are not required to show "epidemiologic studies, rechallenge, the presence of pathologic markers or genetic disposition, or general acceptance in the scientific of medical communities to establish a logical sequence of cause and effect . . . ." Capizzano v. Sec'y of Dep't of Health & Human Servs., 440 F.3d 1317, 1325 (Fed. Cir. 2006). Instead, circumstantial evidence and reliable medical opinions may be sufficient to satisfy the second Althen factor. Capizzano, 440 F.3d at 1325-26; Andreu, 569 F.3d

[21] The distinction between possible causation based on speculation as opposed to facts and reasonable inferences clarifies Dr. Herskowitz's testimony that Dr. Kennedy's theories are "plausible" and "possible." The testimony affirms that science cannot at present show that Dr. Kennedy's theories are impossible or implausible. Tr. at 204. But, clearly, Dr. Herskowitz rejected those theories based on his medical knowledge as an expert. See Tr. at 202.

at 1357 (treating physician testimony). Petitioners' case under Prong 2 was presented through Dr. Kinsbourne, who maintained that Doe suffered a reactivation of a latent HSV-2 infection following her vaccinations in May 2007. For the reasons that follow, Petitioners have not established logical chain of causation under Prong 2.

1. Dr. Marcel Kinsbourne's Opinion

Dr. Marcel Kinsbourne is a pediatric neurologist with a distinguished background, however, he has not treated a patient with HSE in 30 years. Tr. at 117.[22] He reasoned that because HSE is such a rare condition, and Doe did not have a genetic weakness, she must have suffered a "lapse in immunity" because of her vaccinations. Id. at 120-21.

In his expert report, Dr. Kinsbourne described Doe's medical history and the course of her illness and treatment. Dr. Kinsbourne's Expert Report at 1-3 (Pet'r Ex. 16) [hereinafter "Dr. Kinsbourne's Report"]. Dr. Kinsbourne noted that three to six days after her vaccinations on May 2, 2007, Doe "began to have the prodomal symptoms of her encephalopathy." Id. at 3. In Doe's case, according to Dr. Kinsbourne, the vaccinations, "and especially the acellular pertussis and the Prevnar vaccines, are a medically reasonable cause of inflammation that can substantially contribute to the occurrence of the encephalitis by activating a latent [HSV] infection." Id. at 4. He stated that there was no evidence in the record of "alternative triggers that could have reactivated the latent virus infection." Id. He added that the "time interval between vaccination and disease onset was proximate." Id.

Focusing on the results of her serological testing, Dr. Kinsbourne concluded in his report that Doe had an active HSV-1 infection, "whereas her HSV-2 infection was longer term or in the past." Id. at 2. Dr. Kinsbourne described the two serotypes, HSV-1 and HSV-2, stating that HSV-1 causes most of the herpes infections that implicate the brain. Id. at 3. Over a lifetime, HSV-1 "harmlessly colonizes the great majority of people." Id. In its latent state, the virus is non-replicative and protected from immune attack. Id. at 4. He listed some stressors that are known sometimes to result in reactivation, "including fever, irradiation, exposure to ultraviolet light, trauma, psychologic stress and various causes of inflammation." Id. According to Dr. Kinsbourne, the common property of these stressors is "that they all are apt to cause production of proinflammatory cytokines." Id.

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[22] Dr. Kinsbourne's qualifications to offer an opinion as to causation in this case pale by comparison with those of the Secretary's experts. Dr. Kinsbourne is a respected pediatric neurologist but has no special qualifications in treating infectious diseases and has treated no HSE patients in recent decades. Tr. at 116. Dr. Leist is an adult neurologist with an active clinical practice, and he sees children regularly. Tr. at 52. Dr. Klein is a pediatrician who specializes in infectious diseases in infants and children, has been practicing as such for more than 50 years, and continues to see patients at the rate of about 20 per week. Tr. at 155-56. Dr. Klein has treated pediatric patients with HSE from newborns to young adults. Tr. at 156-57. Dr. Herskowitz is a pediatric neurologist who sees between 40 and 50 patients per week. Id. at 187-88.

At hearing, Dr. Kinsbourne "clarified" his causation theory, adopting the "Th-skewing" theory described by Dr. Kennedy during his testimony. Tr. at 123-24. He confirmed that "this child had encephalitis caused by the herpes virus[;] [t]here's no question." Id. at 125-26. He stated that his report identified DTaP as "one of the vaccines" implicated in Doe's disorder, "but actually by the logic of it is what's really applied to any bacterial vaccine." Id. at 126.

Dr. Kinsbourne testified that Doe's laboratory results "are not completely consistent," but the serological testing indicated that, "there had been a prior infection with HSV-2, which was latent, and that the vaccines had reactivated that virus to cause a steep rise in the immune system's response . . ." Tr. at 122-23. Based on the results of the serology and PCR testing, he opined that Doe's HSE was caused by a recurrence of HSV-2. Tr. at 122, 133. Dr. Kinsbourne testified that he was "at a loss to state when exactly this infection took place." Id. at 123. Nonetheless, he stated that he would "assume that indeed it was an HSV-2 infection for purposes of [his] theoretical account." Id. at 122; see id. at 132 (testifying that HSV-2 "seems to fit better into a coherent account of the situation").

Dr. Kinsbourne testified that he did not rule out a primary herpes infection but, based on the serology, "on balance, I would favor recurrence." Tr. 122-23, 126. Asked to explain why, if Doe had a recurrence of a pre-existing herpes infection in May 2007, she did not react adversely to her previous vaccinations, Dr. Kinsbourne could not provide an explanation. Tr. at 127. He stated that other potential triggers of herpes reactivation, like physical trauma or UV light, sometimes will cause an individual to suffer a recurrence, sometimes not, which is not "surprising . . . because that's what happens all the time." Id. at 127.

Dr. Kinsbourne affirmed that the course of Doe's illness was "perfectly congruent with the condition" of herpes encephalitis. Id. at 129. He hypothesized that Doe would not have gotten HSE without having been vaccinated, "because by and large children don't get herpes encephalitis. It's rare, so by my theory, she would not have." Id. at 133. His vague explanation for why more children do not contract herpes encephalitis given the prevalence of the virus and vaccines in early childhood was:

> Clearly, there must be some combination of factors, maybe a combination of the presence of the virus, the immune status of the individual, the co-existence of provocative factors of which maybe vaccination is one, maybe the developmental level of the child and the child, her immune system. I think with something like this you must think of a multidimensional convergence, but clearly we can't precisely stipulate what is was.
>
> . . .
>
> That's not to say that the next child who has herpes virus encephalitis will have had it at the time of vaccination. It could have been some other prerogative factor.

> You see, basically all that says is that in this particular case a reactivation occurred because of a vaccine. In another case, it might have occurred for some other reason, but not in [Doe].

Id. at 134-35.

Dr. Kinsbourne agreed that there is "a lot of uncertainty" concerning the factors that may trigger reactivation of herpes virus, but he stated that the vaccination was "the only reasonable explanation" in Doe's case. Id. at 138. Yet, when asked about a scenario in which Doe's out-of-town trip might have caused "stress" that could have reactivated a latent herpes infection, Dr. Kinsbourne stated that he "wouldn't rule it out." Id. at 139. When asked whether he could explain how stress or infection would reactivate herpes, Dr. Kinsbourne testified that "some of the times they're still involved probably in a way not unlike that which Dr. Kennedy describe[d], [but] I can't take it further." Tr. at 140. In Dr. Kinsbourne's view, "I feel that's not acceptable that just having herpes infection doesn't explain why it goes to the brain and devastates it. We should be looking for something in addition, and whether it's a vaccine or not I don't know, but that's one reasonably possible factor." Id. at 143.

2. Dr. Thomas Leist's Opinion

Dr. Leist is a practicing adult neurologist, but he occasionally sees pediatric neurology cases. Tr. at 52-53. Based on the clinical presentation, the PCR results, the serology tests, and the MRIs, Dr. Leist attributed Doe's encephalitis to a primary HSV-2 infection alone. Dr. Leist's Report at 12; Tr. at 55-56. In Dr. Leist's view, Doe had a primary HSV-2 infection, acquired around the time of her vaccination, although he recognized that there were circumstances concerning some laboratory tests indicating infection with HSV-1 that were puzzling. Tr. at 57-58, 74.

In reaching his conclusion of a primary HSV-2 infection, Dr. Leist emphasized the importance of the test results on Doe's CSF samples. "As a practicing physician, a positive herpes PCR for me is essentially as close to absolute proof as it gets . . . The fact that this was herpes Type 2 has been established to a degree that I don't think I could go beyond." Id. at 69. The PCRs "showed the actual amplifiable DNA of the virus," so the inconsistencies with the serological studies do not "set[] aside the fact that we have on two separate occasions in two individually separately obtained CSF specimens the proven presence of the virus . . . ." Id. at 73-74.

Dr. Leist testified that Doe acquired the HSV-2 virus "before or around" the time of her vaccinations. Id. at 81. He noted that Doe may have had a latent HSV-1 infection before she contracted HSV-2. Id. at 81-82. He also testified that herpes simplex is present in over 80% of the general population, and being herpes simplex positive "is not associated with ill effects during vaccinations." Id. at 82.

Dr. Leist emphasized the fact that "for me this is a primary herpes infection and . . . the course is actually congruent with . . . herpes encephalitis with a normal course." Id. at 59. Dr. Leist stated that Doe did not exhibit any signs or symptoms showing that Dr. Kennedy's theory was at work, such as an immediate reaction to the vaccines or a reaction to prior vaccines. Dr. Leist's Report at 10-11; Tr. at 88-89. "If I look at this particular case, I can explain everything that occurred to this particular child on the basis of primary herpes type 2 infection." Tr. at 88. He noted that there was no evidence of any immune deficiency in Doe's case; Doe was continually exposed to environmentally presented bacteria and viruses that would stimulate her immune system to a Th2 response, such that any immune deficiencies would have manifested prior to the vaccinations. Id. at 59-60. Dr. Leist found it difficult to see why it was only the third administration of the DTaP, Hib, and Prevnar vaccines, which initiated an immune process that occurs frequently in both vaccinated and unvaccinated persons, that caused the putative weakening of Doe's immune system. Id. at 86-89.

3. Dr. Jerome Klein's Opinion

Dr. Klein opined that "[t]his is a typical case of herpes encephalitis . . . ." Id. at 164. Dr. Klein expressed the opinion that Doe's herpes infection was probably primary, because Doe showed no signs of encephalitis before the episode in May 2007. Tr. at 162-64. In his experience, recurrences "mimic" the initial episode. Id. at 163. Therefore, if Doe had previously acquired the herpes virus, there would have been "some antecedent event" of an encephalitic nature in her medical history, which there was not. Id. Dr. Klein testified that, although herpes is a very common cause of serious encephalitis, it is uncommon in a 20-month old. Id. at 165.

4. Dr. Joel Herskowitz's Opinion

Dr. Herskowitz agreed with Dr. Klein that Doe's symptoms were consistent with HSE, and he could find no evidence to indicate that this was anything more than a case of HSE. Dr. Herskowitz's Report at 7; see Tr. at 192 ("Take away the set of immunizations, and the clinical course is fully consistent with herpes encephalitis").

5. Analysis of Prong 2

Petitioners presented no evidence in the medical record pointing to a vaccine reaction as precipitating Doe's illness. Their case was based primarily on the fact that Doe's HSE was so mysterious and rare.[23] It was so rare that Dr. Kinsbourne concluded, reasonably, that there must be some additional factor at work in this particular case that caused Doe to suffer this injury. The problem is that Dr. Kinsbourne's choice of immunization as the culprit lacked any support in the medical record.

[23] Dr. Leist agreed that it is rare for someone Doe's age to contract HSE, and that it is even rarer for someone her age to contract type-2 HSE. Tr. at 58.

Dr. Kinsbourne identified no evidence of inflammation or other symptom consistent with the response to vaccination that he posited as the reason Doe contracted HSE. He identified no evidence that any treating professional associated Doe's vaccination with her illness. The crux of Dr. Kinsbourne's analysis was the lack of any other explanation, at least in his view, for why Doe contracted HSE when she did. Tr. at 133-35. To conclude that, in the absence of any other explanation, vaccination was the cause of Doe's illness is logically flawed and contrary to law. Establishing a logical sequence of cause and effect requires more than a simplistic elimination of other causes. Moberly, 592 F.3d at 1323. Without explanation, Dr. Kinsbourne summarily dismissed other potential factors that, under his own theory, could have precipitated an inflammatory reaction leading to reactivation of a latent herpes infection. See, e.g., Tr. at 127; Dr. Kinsbourne's Report at 4 (infection, physical trauma, psychological stress); Pet'r Ex. 6 at 5, 48 (away from home at time of onset); id. at 48 (mother's report of possible reaction to eating fried seafood day prior to first admission to hospital); id. at 51 (scratched by cat just before going on trip).

At hearing, Dr. Kinsbourne was asked whether the facts that Doe had traveled from home and was in a strange environment, among people she was not accustomed to, could have resulted in the kind of stress that might lead to reactivation of a herpes infection. Dr. Kinsbourne did not reject the suggestion. See Tr. at 139. He could not do so because, under his theory, any stressor could have provoked the herpes reactivation. Based on Dr. Kinsbourne's testimony, there was no more reason to suspect that Doe's illness was precipitated by the vaccinations than there was to suspect that it was precipitated by the cat scratch she suffered, the sea food she consumed, or the psychological stress of travel, being in a strange place, and interacting with strangers.

Dr. Kinsbourne's opinion also suffered from internal contradictions. His expert report stated that Doe's encephalitis resulted from an inflammatory reaction, but after listening to Dr. Kennedy's testimony at hearing, Dr. Kinsbourne "clarified" his opinion and adopted the "Th-skewing" hypothesis. Dr. Kinsbourne's Report at 4; Tr. at 123-24. While his report relied on evidence of an inflammatory reaction, he testified that the medical record noted no inflammation at the site of Doe's vaccinations. Tr. at 131. Doe had no fever until five days after her vaccinations, and Dr. Kinsbourne admitted that this fever was consistent with HSE. Tr. at 129. Dr. Kinsbourne identified HSV-1 as the culpable virus in his report, while at hearing he identified it as HSV-2. Tr. at 132; Dr. Kinsbourne's Report at 2. He offered no explanation for the change.

Dr. Kinsbourne's testimony was unpersuasive for additional reasons. He interpreted Doe's serology as establishing that she likely had a recurrent, rather than a primary, HSV infection, but he recognized that the serological results were flawed. Tr. at 121-23. When the underpinning of "recurrent" infection theory, namely, dubious test results, is removed from Dr. Kinsbourne's opinion, there is very little factual evidence remaining to substantiate his assertion that a recurrent infection caused Doe's injury. See Menkes at 483 (serological testing much less reliable than PCR in herpes cases); Tr. at 35 (Dr. Kennedy testified that the only evidence of

recurrence is the serology).

In sum, Dr. Kinsbourne's testimony created a tangled skein of "possibilities," not a coherent sequence of facts. Dr. Kinsbourne's opinion is best summarized in his own words: Doe's illness was caused by something "in addition [to the virus], and whether it's a vaccine or not I don't know, but that's one reasonably possible factor." Tr. at 143. And as for why other children do not respond to vaccinations as Doe did, "with something like this you must think of a multidimensional convergence [of factors], but clearly we can't precisely stipulate what it was." Tr. at 134. Prong 2 of Althen requires a logical explanation grounded in medical facts, demonstrating cause and effect in the case before the Court. Dr. Kinsbourne's opinion was too contradictory and ambiguous to satisfy this requirement.

D. Petitioners' Evidence of Appropriate Timing – Prong 3

To show causation, a petitioner must establish that the injury occurred within a time frame that is consistent with the theory of causation set forth. Pafford, 451 F.3d at 1358. A temporal relationship between receipt of a vaccine and the alleged onset of symptoms, without more, however, is insufficient to establish a causal relationship in a cause-in-fact case. Grant, 956 F.2d at 1148. What constitutes an appropriate temporal association is a question of fact and will vary with the particular theory of causation advanced. Id.; de Bazan, 539 F.3d at 1352. Evidence showing the injury occurred in a medically acceptable time frame "is even more important in cases involving contemporaneous events other than the vaccination, because the presence of multiple potential causative agents makes it difficult to attribute 'but-for' causation to the vaccination." Pafford, 451 F.3d at 1358.

Petitioners presented scant evidence regarding a medically appropriate timing of onset. Dr. Kinsbourne appeared to rely on Dr. Kennedy's opinion in relation to timing. Tr. at 123 (stating that the virus was activated at the same time as the "Th-skewing . . . as Dr. Kennedy described and on whose description I rely in this respect"). It is not clear, however, when Th-skewing occurred, since Dr. Kennedy never described how long it would take for the phenomenon to occur. Nor is it clear how long the skewing would last or how long the body would be weakened to viruses. With regard to Dr. Kennedy's other theory, the medical record does not show inflammation following the vaccination and shows fever only five days later, when fever was, according to Dr. Kinsbourne's testimony, "perfectly congruent" with herpes infection. Tr at 129. On these facts, one cannot say that Petitioners have established a medically appropriate timing of onset. Doe indeed became ill several days after being vaccinated. That in itself is not sufficient to establish causation. See Pafford, 451 F.3d at 1358.[24]

[24] Dr. Leist explained that HSV-2, which most commonly is sexually transmitted, normally is not acquired by a young child unless there are lesions present in the mother at the time of delivery. Since there was no indication of transmission during delivery in Doe's case, Dr. Leist concluded that Doe probably acquired the virus later, "around the time of the vaccination" by coming into contact with someone or some thing that transmitted the virus. Tr. at 58. This is a more logical sequence of cause and

In sum, none of the Althen factors has been satisfied here, and Petitioners have failed to establish a prima facie case of vaccine causation. If the petitioner fails to establish a prima facie case of causation, the burden does not shift to Respondent. See, e.g., Bradley v. Sec'y of Dep't of Health & Human Servs., 991 F.2d 1570, 1575 (Fed. Cir. 1993) (when petitioner has failed to demonstrate causation by a preponderance, alternative theories of causation need not be addressed).

IV. CONCLUSION

Based on the entire record, Petitioners have not presented a prima facie case of vaccine causation-in-fact. Therefore, Respondent is entitled to judgment.

For the foregoing reasons, Petitioners' Petition for compensation is **DISMISSED**. In the absence of a motion for review, the Clerk shall enter judgment accordingly.

IT IS SO ORDERED.

s/ Dee Lord
Dee Lord
Chief Special Master

effect than Dr. Kinsbourne's theory that Doe suffered an HSV-2 infection earlier in her young life, and that the virus had been activated only at the time of her vaccinations in May 2007 (but not at the time of her previous vaccinations, when she exhibited no adverse vaccine reactions).