In the United States Court of Federal Claims
OFFICE OF SPECIAL MASTERS

* *		
JESSIE CONTRERAS,	*	
	*	
Petitioner,	*	No. 05-626V
	*	Special Master Christian J. Moran
v.	*	
	*	Filed: November 19, 2013
SECRETARY OF HEALTH	*	
AND HUMAN SERVICES,	*	hepatitis B vaccine; tetanus-diphtheria
	*	vaccine; transverse myelitis (TM);
Respondent.	*	Guillain-Barré syndrome (GBS);
	*	one-day onset; decision on remand
* *		

Jeffrey S. Pop, Jeffrey S. Pop, Attorney at Law, Beverly Hills, CA, for petitioner;
Linda S. Renzi, United States Dep't of Justice, Washington, DC, for respondent.

PUBLISHED DECISION ON REMAND DENYING ENTITLEMENT[1]

I. Introduction

Jessie Contreras alleges that either a hepatitis B vaccination and/or a tetanus-diphtheria (Td) vaccination caused him to develop a neurological problem that began one day after his vaccinations. His case is proceeding in the National Childhood Vaccine Injury Compensation Program. 42 U.S.C. § 300aa-10 et seq. (2006). The statute authorizes recovery when the petitioners establish that vaccines caused a new illness or significantly aggravated a preexisting one.

An April 5, 2012 decision found that Mr. Contreras failed to establish that either the hepatitis B or Td vaccine caused his illness based on a failure to establish one of the factors set forth in Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274 (Fed. Cir. 2005), namely, that one day between vaccination and onset of symptoms constitutes a medically appropriate temporal relationship from which causation can be inferred. Contreras v. Sec'y of Health & Human Servs., No. 05-626V, 2012 WL 1441315, at *1 (Fed. Cl. Spec. Mstr. Apr. 5. 2012)

[1] The E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (Dec. 17, 2002), requires that the Court post this decision on its website. Pursuant to Vaccine Rule 18(b), the parties have 14 days to file a motion proposing redaction of medical information or other information described in 42 U.S.C. § 300aa-12(d)(4). Any redactions ordered by the special master will appear in the document posted on the website.

(Entitlement Decision). The Entitlement Decision did not address the two other Althen prongs because Mr. Contreras's failure on the timing aspect was a sufficient basis to deny compensation.

Mr. Contreras filed a motion for review with the Court of Federal Claims (the Court). On September 28, 2012, the Court granted petitioner's motion, vacated the Entitlement Decision, and "remand[ed] for proceedings in accordance with the principles of law and the instructions set forth in [its] opinion." Contreras v. Sec'y of Health & Human Servs., 107 Fed. Cl. 280, 283 (2012) (Opinion and Order).

The parties filed briefs on remand that addressed the record and the Court's Opinion and Order, but no new evidence. Hence, the previously submitted evidence is reviewed in light of the Court's instructions on remand.

After additional consideration, the undersigned finds that Mr. Contreras has failed to establish by a preponderance of the evidence that he is entitled to compensation. First, he has not provided preponderant evidence to demonstrate that the hepatitis B vaccine can cause transverse myelitis[2] via his expert's proposed mechanism of causation, molecular mimicry. Second, a preponderance of the evidence demonstrates that transverse myelitis cannot manifest via molecular mimicry within one day.

II. Facts

The record includes much testimony, presented either in writing or orally, from doctors. Some doctors treated Mr. Contreras and some doctors were retained particularly for this litigation. A synopsis of their qualifications is presented first as a matter of background in section II.A.

Collectively, the doctors' testimony helped explain what happened to Mr. Contreras and, thus, their comments are interspersed in the discussion about Mr. Contreras's medical history. Relevant information for this decision includes Mr. Contreras's health before and after he was vaccinated. His history is summarized in section II.C, below, which is preceded in section II.B by a general discussion about two conditions that arguably afflicted Mr. Contreras, transverse myelitis and Guillain-Barré syndrome (GBS). This background information about transverse myelitis and GBS provides a context for understanding the significance of events in Mr. Contreras's health history.

[2] Mr. Contreras alleged that he developed both transverse myelitis and Guillain-Barré Syndrome (GBS). As discussed in detail below, a preponderance of the evidence indicates that he suffered from transverse myelitis only. Accordingly, this decision focuses on whether the hepatitis B vaccine and/or the Td vaccine can (and did) cause transverse myelitis in approximately one day.

A. Mr. Contreras's Treating Physicians and the Parties' Specially Retained Experts

Mr. Contreras offered the testimony of three of his treating physicians, Dr. Fred Kyazze, Dr. Jeremy Garrett, and Dr. Mark Wagner. Mr. Contreras also offered the testimony of Dr. Lawrence Steinman and Dr. Charles Poser, whom he retained as experts in support of his claim. The Secretary offered testimony from Dr. John Sladky and Dr. Lindsay Whitton, whom she retained in this litigation.

1. Dr. Kyazze

Mr. Contreras submitted a short affidavit from Dr. Kyazze (exhibit 11), who testified at the April 19, 2010 hearing. Tr. 41. Dr. Kyazze administered Mr. Contreras's subject vaccinations on June 16, 2003, and also examined Mr. Contreras.

Dr. Kyazze received an undergraduate degree in biology from Occidental College in Los Angeles, California, and attended medical school at Makerere University in Uganda. He completed a residency in family medicine and later became board-certified in that specialty. Tr. 42.

2. Dr. Wagner

Dr. Wagner treated Mr. Contreras for approximately five hours of his first emergency room admission on June 17, 2003. Exhibit 12 at 2, ¶ 13; exhibit 6 at 9; Tr. 66-69. Dr. Wagner submitted an affidavit (exhibit 12) and testified at the April 19, 2010 hearing on Mr. Contreras's behalf. Tr. 63.

Dr. Wagner received undergraduate degrees in biology and chemistry from the University of California at Irvine, and a medical degree from the University of California at Los Angeles. Tr. 63. He then completed a residency in emergency medicine and later became board-certified in that specialty. Tr. 63. He has been practicing medicine for more than 30 years. Tr. 64.

3. Dr. Garrett

Dr. Garrett was Mr. Contreras's attending physician during his lengthy hospitalization immediately following the onset of his neurological problems. Exhibit 7 at 157. Dr. Garrett, as discussed below, consulted with other doctors to care for Mr. Contreras.

Dr. Garrett submitted an affidavit (exhibit 13) on Mr. Contreras's behalf, but was unable to testify in person. Tr. 101. He received his bachelor's degree from Northwestern University and his medical degree from the University of Nebraska. Exhibit 127 at 1. He then completed a residency in pediatrics and a fellowship in pediatric critical care. Id. He has held numerous professorships in the fields of pediatrics. Id.

At the time he submitted his affidavit, Dr. Garrett was board-certified in general pediatrics and pediatric critical care medicine, and was a professor of pediatrics at the Saint Louis University School of Medicine. Exhibit 13 at 1-2. He also had an active clinical practice. Id. at 2; exhibit 147 at 2.

4. Dr. Poser

Mr. Contreras retained Dr. Poser to testify on his behalf. Dr. Poser submitted two affidavits (exhibits 22 and 23), but was unable to testify. Tr. 102; see also Opinion and Order, 107 Fed. Cl. at 283 n.5.

Dr. Poser received his bachelor's degree from the College of the City of New York and his medical degree from Columbia University. Exhibit 126 at 1. He then completed a residency in neurology. Id. Dr. Poser held numerous professorships and professional positions in the field of neurology. Id. at 1-2. At the time he submitted his affidavits, he was board-certified in neurology and child neurology. Dr. Poser was also retired (exhibit 22 at 1, ¶ 12), with approximately 50 years of clinical experience. Exhibit 23 at 6, ¶ 13.

5. Dr. Steinman

Dr. Steinman testified for Mr. Contreras as an expert in neurology. Dr. Steinman prepared four reports with numerous pieces of literature to support his opinions. See exhibits 55, 105, 124, and 152. He also testified at the hearings on April 19-20, 2010, and July 24, 2011.

Dr. Steinman is a professor in Stanford University's Departments of Neurology and Neurological Sciences, Pediatrics and Genetics. He chairs that institution's program in immunology. He has substantial research experience and has published extensively in the fields of neurology and immunology. He has received national and international honors for his work in researching multiple sclerosis. Exhibit 56 (curriculum vitae).

6. Dr. Sladky

Dr. Sladky testified for the Secretary as an expert in neurology. He received his bachelor's degree and medical degree from Yale University. Exhibit J (Dr. Sladky's curriculum vitae) at 1. He completed a residency in pediatrics at Yale-New Haven Hospital and then completed a fellowship in neurology at the Children's Hospital of Philadelphia. Id. He is board-certified in pediatrics, psychiatry, and neurology with special competence in child neurology and electric diagnostic medicine. Id.; Tr. 276. His CV, which appeared to have been created in 1999 and was filed in 2005, indicated that he was licensed in Pennsylvania and Georgia. Exhibit J at 2.

Dr. Sladky has been a part of the faculty at Emory University School of Medicine since 1995. He has been the chief of the Division of Pediatric Neurology, as well as a professor in the departments of pediatrics and neurology. Exhibit J at 2, 3.

At the hearing, Dr. Sladky explained what his duties at Emory were. He stated that he spends half of his time teaching and the other half performing clinical work. He "see[s] patients every week, usually five half days a week, probably [an] average [of] 40-50 patients a week." Tr. 275. His teaching duties involve giving clinical lectures to medical students, residents, and fellows. Tr. 276. At the hearing, Mr. Contreras did not challenge Dr. Sladky's qualifications, Tr. 278, and he was accepted as an expert in pediatric neurology. Tr. 278.

During the pendency of this decision on remand, the Secretary filed a status report

> to disclose to the court . . . [that the Secretary] ha[d] become aware that Dr. Sladky agreed not to practice medicine in the [S]tate of Georgia from August 19, 2008 to March 18, 2009, and agreed to the indefinite suspension of his license to practice medicine on June 17, 2009, and that on March 4, 2010, the suspension of his license was lifted and his license to practice restored on a probationary basis. The probation was terminated on July 5, 2011.

Resp't's Status Rep't, filed May 1, 2013, at 1. Dr. Sladky's license had been suspended and he had been placed on probation due to alcohol abuse problems. See id. at 4. The Secretary attached supporting documentation to her status report to verify the dates during which Dr. Sladky's license had been suspended and he had been on probation. Neither the parties nor their counsel were aware that Dr. Sladky's license had been suspended or that he had been on probation when he had provided expert witness services during the course of this proceeding.

After the Secretary disclosed these facts about Dr. Sladky's licensing, Mr. Contreras filed a status report, arguing that Dr. Sladky's testimony should "carry little, if any weight, due to the circumstances under which he was providing testimony." Pet'r's Status Rep't, filed May 10, 2013, at 9. Mr. Contreras also indicated that Dr. Sladky's CV inaccurately stated that he was licensed in Pennsylvania, although that license had expired in 1996. See id. at 4, 15.

The thrust of Mr. Contreras's argument is that Dr. Sladky's testimony is unreliable because he had an alcohol problem[3] at all relevant times, he misled the court in describing his clinical research and job responsibilities at Emory University when he testified at the hearing, and he violated the terms of his probation by testifying. Id. at 3, 7. Mr. Contreras asserted that Dr. Sladky's substance abuse problems implicated "his physical condition as well as intellectual processing ability" and his license suspension and probation led him to testify on behalf of the Secretary for financial reasons. Id. at 9-10.

Pursuant to the parties' agreement reached at a status conference held on May 20, 2013, the Secretary filed a response to Mr. Contreras's arguments regarding Dr. Sladky. See Order,

[3] Mr. Contreras stated that Dr. Sladky suffered from an additional problem. However, there is nothing in the record to support this assertion.

filed May 20, 2013; Resp't's Br. on Remand, filed June 12, 2013. The Secretary argued that Dr. Sladky's licensure issues did not affect the validity or value of his opinions.

First, the Secretary asserted Dr. Sladky did not misrepresent the nature of his professional responsibilities at Emory University when he testified at the hearing. Resp't's Br. on Remand at 37. The Secretary noted that Dr. Sladky's license suspension had been removed prior to the hearing and asserted that Mr. Contreras has no evidence to demonstrate that Dr. Sladky's testimony regarding his professional responsibilities at Emory University was untrue or misleading. Id. Second, the Secretary suggested that Mr. Contreras's argument that Dr. Sladky's testimony was financially motivated should be stricken from the record because it is "disingenuous." Id. at 37-38. The Secretary pointed out that Dr. Sladky's opinion in this matter had been consistent since 2005, years before he had any licensure issues, and Mr. Contreras has no basis to argue Dr. Sladky's income had been affected by his licensure issues. Id. Finally, the Secretary asserted that Mr. Contreras has no evidence to demonstrate that Dr. Sladky's testifying in this matter violated the terms of his probation. Id. at 38. For these reasons, the Secretary argued that Dr. Sladky's undisclosed licensure issues should not affect the evidentiary weight of his opinions. Id. at 39.

Mr. Contreras responded to the Secretary's arguments in his reply brief on remand. See Pet'r's Reply Br. on Remand, filed Aug. 13, 2013, at 31-34. Mr. Contreras indicated that the Secretary did not respond to four issues regarding Dr. Sladky that he mentioned in his May 10, 2013 status report. Id. at 31-32. Mr. Contreras pointed out that the Secretary did not explain why Dr. Sladky: (1) failed to disclose his licensure issues; (2) did not indicate in his CV that his Pennsylvania license had been inactive since 1996; (3) worked on his March 4, 2010 report, when his license was suspended; and (4) worked on other cases within the Program when his license was suspended and when he was on probation. Id. Mr. Contreras argued that "Dr. Sladky's lack of transparency and untruthfulness . . . bear on his bias and character critically undermining his credibility as an expert." Id. at 34. Mr. Contreras concluded that these issues with Dr. Sladky's licensure should "result in [Dr. Sladky's] testimony being scrutinized and given diminished importance." Id.

As the Secretary correctly pointed out, Dr. Sladky's opinion has been consistent since his initial report, filed on October 27, 2005, which predates any licensure issue by almost three years. See Exhibit I. In that report, Dr. Sladky opined that Mr. Contreras's injury "was, almost certainly, transverse myelitis." Id. at 2. He opined that the onset of Mr. Contreras's transverse myelitis within 24 hours after his vaccinations was "purely coincidental" because it would be "virtually impossible" for a vaccine to trigger "an immunological attack on the nervous system… within a 24 hour interval." Id. at 3. He claimed that such a process would take at least five days. Id. Further, he disputed whether the hepatitis B vaccine can cause transverse myelitis. Id. at 4.

As to the dates when Dr. Sladky was working as an expert, Mr. Contreras has not established that a suspension of a license to practice medicine means that the person may not provide opinions based upon the person's training and experience. Dr. Sladky's writing of a report in this case did not entail him seeing Mr. Contreras as a patient.

With regard to his Pennsylvania licensure, Dr. Sladky's CV, which was prepared in 1999, contained an error because his license expired in 1996. See exhibit J at 1. Whether this error occurred due to forgetfulness or due to intent is difficult to say. At the hearing, Dr. Sladky did not state that he was licensed to practice medicine in Pennsylvania. In fact, he was not asked where he was licensed at the time.

The Secretary does not dispute that Dr. Sladky should have disclosed the information concerning his health issues and the effect they had on his ability to practice medicine. The failure to disclose this important information bears on his credibility and reliability as an expert witness. See Mousseau v. Schwartz, 756 N.W.2d 345, 360 (S. D. 2008); George L. Blum, Annotation, Propriety of questioning expert witness regarding specific incidents or allegations of expert's unprofessional conduct or professional negligence, 11 A.L.R.5th 1 (1993).

However, the lack of disclosure and (implicit) misrepresentation about qualifications does not entirely negate Dr. Sladky's opinion. Dr. Sladky established his opinion almost three years before his license was suspended and it has not changed throughout the course of these proceedings. As the Secretary asserted, it does not appear that Dr. Sladky's personal health issues or his licensure problems affected his opinions in any way. In addition, Dr. Sladky's opinions are consistent with the opinions of other witnesses. This corroboration shows that Dr. Sladky's opinions retain some value.[4]

7. Dr. Whitton

Dr. Whitton testified for the Secretary as an expert in immunology. Dr. Whitton submitted four expert reports (exhibits L, N, U, and BB) and testified at the April 20, 2010 and July 28, 2011 hearings. Tr. 405, 621. Dr. Whitton received his bachelor's degree in molecular biology, his medical degree, and his Ph.D. from the University of Glasgow, Scotland. Exhibit M at 1. He does not treat patients in the United States and is not licensed to practice medicine in the United States. See Opinion and Order, 107 Fed. Cl. at 286 n.14. He has held a number of professorships and professional positions in the field of immunology. He has substantial research experience and has published extensively in the fields of immunology and virology. Exhibit M at 1-12. Since 2008, he has been a professor at Scripps Research Institute in the Department of Immunology and Microbial Science. Id. at 1.

B. Overview of Transverse Myelitis and Guillain-Barré Syndrome

As explained below, there is universal consensus that Mr. Contreras suffered from transverse myelitis. All of the doctors who treated Mr. Contreras diagnosed him with transverse myelitis. The doctors whom Mr. Contreras retained for this litigation diagnosed him with

[4] As discussed more extensively below, one of the issues is diagnosis. On this topic, Dr. Sladky's opinion matches the diagnosis of Mr. Contreras's treating neurologist. Another issue concerns the effect, if any, of the vaccinations. On this topic, Dr. Sladky's opinion is similar to Dr. Whitton's opinion.

transverse myelitis. The doctors whom the Secretary retained for this litigation also diagnosed him with transverse myelitis.

The complicating factor is that some treating doctors initially considered the possibility that Mr. Contreras suffered from another disease, GBS. Mr. Contreras's specially retained doctors advanced the position that Mr. Contreras suffered from both transverse myelitis and GBS. However, one of the doctors retained by the Secretary disagreed and opined that Mr. Contreras never suffered from GBS and suffered from transverse myelitis only.

Because there is no dispute that Mr. Contreras suffers from transverse myelitis, transverse myelitis is described first in section 1. The following section discusses GBS. Finally, section 3 presents some information about how these two diseases are caused. The section on etiology is relatively brief because the analysis of whether vaccines can cause these conditions is discussed in greater detail in section V.B.

1. Transverse Myelitis

Transverse myelitis is an autoimmune condition in which inflammation causes damage to the spinal cord. See Tr. 125, 315, 414. The clinical presentation often develops suddenly and is usually marked by bladder and bowel problems, a loss of movements in the legs, and numbness. See exhibit N, tab 2 (Douglas A. Kerr & Harold Ayetey, Immunopathogenesis of Acute Transverse Myelitis, 15(3) Current Opinion in Neurology 339 (2002)) at 339-40. "Back and sometimes radicular pain are often the first symptoms." Exhibit 29 (L. Reik, Jr., Neurological complications of immunization, 2 Neurological Infections & Epidemiology 69 (1997)) at 75. "Although all functions of spinal cord may be disturbed, different degrees of disability occur. It has been observed that functional recovery depends much on the clinical presentation; an abrupt and severe onset usually pointing to a poorer prognosis." Exhibit 16 (Luiz Fernando Fonseca et al., Early-Onset Acute Transverse Myelitis Following Hepatitis B Vaccination and Respiratory Infection, 61 Arq Neuropsiquiatr 265 (2003)) at 1-2. Magnetic resonance imaging (MRI) of the spine is used to diagnose transverse myelitis and will show evidence of acute inflammation. Exhibit N, tab 2 (Kerr & Ayetey) at 340.

What causes transverse myelitis is generally not known. Exhibit N, tab 2 at 339 (stating that for acute transverse myelitis "[i]t is unclear what are the triggers and effector mechanisms"). One article suggest that transverse myelitis can be caused by "a direct infection, a systemic disease or an autoimmune (post-infectious or post-vaccinal) process." Exhibit 16 at 3.

Patients with transverse myelitis are usually prescribed steroids. Exhibit 29 at 76. They are also often treated with intravenous immunoglobulin (IVIG). See Tr. 185.

2. Guillain-Barré Syndrome

Guillain-Barré Syndrome is "an immune-mediated peripheral nervous system . . . disease that results in a direct destruction of the myelin sheath or the axon itself." Exhibit L, tab 12 (Ami Schattner, Consequence of coincidence? The occurrence, pathogenesis and significance of autoimmune manifestations after viral vaccines, 23 Vaccine 3876 (2005)) at 3879. It is a disease

that is "usually manifested by a rapidly evolving symmetric and ascending motor paralysis, with loss of tendon reflexes." Exhibit L, tab 22 (M. Khamaisi et al., Guillain-Barré syndrome following hepatitis B vaccination, 22 Clinical & Experimental Rheumatology 767 (2004)) at 767. Individuals afflicted with GBS present

> with paresthesias of the feet, followed by flaccid paralysis of the entire lower limbs, ascending to the trunk, upper limbs, and face; other characteristics include slight fever, bulbar palsy, absent or lessened tendon reflexes, and increased protein in the cerebrospinal fluid without a corresponding increase in cells.

Dorland's Illustrated Medical Dictionary (32d ed. 2012) (Dorland's) at 1832. GBS "is diagnosed by clinical symptoms, such as progressive muscle weakness and loss or decreased level of deep tendon reflex." Exhibit L, tab 10 (Tetsuo Nakayama & Kazumasa Onoda, Vaccine adverse events reported in post-marketing study of the Kitasato Institute from 1994 to 2004, 25 Vaccine 570 (2007)) at 572. The disease "progresses for up to 4 weeks and then reaches a plateau." Exhibit N, tab 7 (Richard A.C. Hughes & Jeremy H. Rees, Clinical and Epidemiologic Features of Guillain-Barré Syndrome, 176 J. Infectious Diseases S92, S92 (1997)). Patients with GBS are often treated with, among other things, IVIG. See exhibit 111 (R.A.C. Hughes et al., Practice parameter: Immunotherapy for Guillain-Barré syndrome, 61 Neurology 736 (2003)) at 737-39; see also Tr. 184.

3. Etiologies for Autoimmune Diseases

As mentioned, both transverse myelitis and GBS are categorized as autoimmune diseases. The basis for an autoimmune disease is a malfunction in the immune system.

A healthy immune system protects the body. Cells in the immune system circulate throughout the body, examining molecules to determine whether the molecule is part of the body (self) or is foreign to the body (an antigen). This determination is made by examining specific sequences of a few amino acids, known as a peptide. When a patrolling cell of the immune system identifies a foreign peptide, this cell recruits other parts of the immune system to destroy the foreign antigen. Tr. 127-30; exhibit 63 (Lawrence Steinman, Autoimmune Disease: Misguided Assaults on the Self Produce Multiple Sclerosis, Juvenile Diabetes and Other Chronic Illnesses. Promising Therapies Are Emerging, Scientific Amer. 107 (1993)) and exhibit 143 (extract from exhibit 63). The destructive part of the adaptive immune system is divided into two types of cells: B cells (also known as antibodies) and T cells.

However, the B cells and T cells can deviate from their normal function by attacking their host. This produces autoimmune diseases, such as transverse myelitis. Tr. 124-25.

Molecular mimicry is an attempt to explain why the immune system goes awry. It posits that an antigen contains a sequence of amino acids that resembles (or mimics) a sequence of amino acids that is similar to a sequence of amino acids normally present in the host. When the immune system responds to the antigen, the destructive T cells mistakenly are directed against the body's own tissue.

To this basic outline about molecular mimicry, Dr. Whitton provided additional details. Dr. Whitton explained that multiple steps comprise molecular mimicry. Dr. Whitton stated:

> If the vaccine-induced T cells are to have caused disease, the following must have happened. (i) The vaccine was injected at a peripheral site (arm/leg). (ii) The vaccine antigens were carried to a lymph node; (iii) in the node, the memory T cells (induced by the previous vaccinations . . .) must have (iv) recognized the antigen, (v) divided and (vi) moved to the sites where disease occurred, in this case the cervical spinal cord (to cause transverse myelitis), and some peripheral nerves (to cause GBS-like disease). . . . Once they reached the sites the T cells would (vii) have to recognize the putative (but unidentified) cross-reactive antigen, and (viii) activate their so-called 'effector functions' to cause harm to the nerve cells. And (ix) it seems reasonable to propose that a fairly large number of T cells would need to accumulate in the spinal cord / peripheral nerves, in order to cause the serious signs and symptoms Jessie showed less than 24 hours after vaccination.

Exhibit L at 9. In reference to this sequence of steps, Dr. Steinman testified that "Dr. Whitton is entirely right." Tr. 240.[5]

The antigens that trigger transverse myelitis or GBS are not known. Frequently, viruses or bacteria, which cause infections, are postulated as a cause for transverse myelitis or GBS. However, these potential causative agents have not been established. Consequently, the testifying experts agreed that the cause (or causes) of transverse myelitis is not known in many cases. Tr. 264, 267, 300, 414.

In this particular case, Dr. Steinman identifies the hepatitis B vaccine as the triggering antigen and a portion of Mr. Contreras's spinal cord, known as myelin, as the tissue that is attacked. Tr. 123-24. The basis and evaluation of Dr. Steinman's opinion is discussed throughout section V.

C. Mr. Contreras's Medical History

The parties do not dispute the accuracy of medical records created contemporaneously with the events being described in those records. These records are the basis for the following facts.

Mr. Contreras was born in 1990. For his first 13 years, Mr. Contreras was generally healthy, see exhibit 3 and exhibit 4, and respondent has not suggested that any early illness

[5] In this portion of Dr. Steinman's testimony, he was also addressing his analogy to the tuberculin skin test.

contributed to his development of the neurological disorder. See Resp't's Post-Hearing Br., filed Nov. 24, 2010. In this time, Mr. Contreras received doses of the diphtheria-tetanus-pertussis vaccine on May 12, 1990, September 5, 1990, February 12, 1991, January 20, 1993, and September 2, 1994. Exhibit 4 at 5, 7-9; petition, filed June 15, 2005, at ¶¶ 5-9. He did not experience any adverse reaction to these five doses. Similarly, Mr. Contreras received two doses of the hepatitis B vaccine (the first on January 23, 2001, and the second on August 23, 2001) without any adverse reaction.

On June 16, 2003, Mr. Contreras saw his pediatrician, Dr. Fred Kyazze, for a routine examination during which he was given a hepatitis B vaccination and a tetanus-diphtheria vaccination. Exhibit 4 at 5, 44. This was the sixth time that Mr. Contreras had encountered some form of the tetanus-diphtheria vaccine and the third dose of the hepatitis B vaccine. Dr. Kyazze administered the vaccinations at approximately 10:30 A.M.

Shortly before noon on June 17, 2003, Mr. Contreras started crying and told his mother that he felt bad. He complained that his hands were numb and that he had "a strong pain in his back." Tr. 15-16. After Mr. Contreras's mother reported these problems to his pediatrician, she was instructed to take her son to the nearest emergency room, which was Memorial Hospital of Gardena in Gardena, California. Exhibit 8 (affidavit of Rosa Contreras) ¶ 26.

When Mr. Contreras left his home for the emergency room with his parents, he walked to his family's car without assistance. During the car trip, he could not maintain his balance and his mother moved from the front seat to the rear seat to help him. When the family arrived at the emergency room, Mr. Contreras vomited in the parking lot twice. His mother and father carried him to the emergency room because he could not walk. Tr. 17.

In the emergency room, Mr. Contreras was seen by Mark Wagner, who testified at the hearing in this case. Dr. Wagner is board-certified in emergency medicine. Dr. Wagner noted that Mr. Contreras had weakness in his arms and legs, was retaining urine, and had priapism. Exhibit 6 at 5-10; see also Tr. 82. A computed tomography (CT) scan of his head and cervical spine was normal. A MRI of his cervical spine was also normal. Exhibit 6 at 15-18. An MRI of his chest was negative. Exhibit 6 at 14. Dr. Wagner's physical examination showed that Mr. Contreras's sense of light touching was altered. Id. at 10. Dr. Wagner also testified that Mr. Contreras's foot turned downward in response to a Babinski test he performed on Mr. Contreras on June 17, 2003. Tr. 78 (citing exhibit 6 at 10).[6]

[6] Dr. Steinman explained that one part of a neurologic examination, a Babinski test, involves running a sharp metal object along the lateral side of the patient's foot to observe how their big toe responds. Tr. 121; see also Dorland's at 1611.

The experts disagreed about the significance of the results of the Babinski test. Dr. Steinman stated that Mr. Contreras's turning his toes downward meant that he had GBS. Tr. 121. But, Dr. Sladky disagreed with Dr. Steinman's opinion that the results of Mr. Contreras's Babinski reflex test were indicative of GBS. Tr. 283.

Dr. Wagner stated at the time of treatment that Mr. Contreras could have atypical GBS, transverse myelitis, and priapism. Exhibit 6 at 5, 10; Tr. 84. When Dr. Wagner treated Mr. Contreras on June 17, 2003, Dr. Wagner did not offer any opinion as to the cause of Mr. Contreras's problems. See exhibit 6. Later, Dr. Wagner offered the opinion in this litigation that the hepatitis B vaccine caused Mr. Contreras's neurological problem. Tr. 89-92.

After remaining in Gardena Memorial Hospital for approximately two-and-a-half hours, Mr. Contreras was transferred by ambulance to a higher care facility, Long Beach Memorial Hospital, which is also known as Miller Children's Hospital. Exhibit 6 at 5. Mr. Contreras remained in this facility until he was discharged on September 11, 2003. Exhibit 13 at 3, ¶ 5. The history at Miller Children's Hospital taken at admission, exhibit 7 at 6, is consistent with the facts set forth above.

When Mr. Contreras arrived at Miller Children's Hospital, the admitting doctor was Christopher Babbitt.[7] Among the first orders given by Dr. Babbitt was a request that Dr. Jean Lake, a neurologist, see a 13-year-old with "weakness and ? Guillain Barre." Exhibit 7 at 1377.[8] Dr. Lake saw him approximately two hours later, which was 8:00 P.M.

Dr. Lake's handwritten notes are generally consistent with the history described above. Dr. Lake recorded that Mr. Contreras "denies any recent infections or fever. He did have dt and hepatitis B vaccine yesterday." Dr. Lake also conducted a neurologic and physical examination. As part of this examination, Dr. Lake recorded that Mr. Contreras's "plantar reflexes [were] ↓↓."[9] Dr. Lake noted that Mr. Contreras's CT scans and MRI at Gardena were negative. See exhibit 7 at 1735. Her impression was "probable atypical Gullain-Barré." Exhibit 7 at 1735. The differential diagnoses included "ADEM [and] transverse myelitis (though there are no sensory abnormalities). MS is also a possibility, though unlikely [with] this clinical presentation." Dr. Lake ordered a lumbar puncture as well as MRIs of the brain and complete spine. Dr. Lake also ordered "IVIG tonight [and] tomorrow [with] total dose 2 gm/kg. Though I would prefer plasmapheresis,[10] I spoke tonight [with] Dr. Brachenburg from the Blood Bank who stated this could not be arranged before tomorrow as we use an outside service. I prefer not to wait until tomorrow to begin treatment given the rapid progression of his neurologic deficit." Exhibit 7 at 1727-28, 1734-35.

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[7] It appears that Dr. Babbitt was the resident initially in charge of Mr. Contreras's care. Dr. Garrett was the attending physician. Exhibit 7 at 157.

[8] Entries from Miller Children's Hospital are typically made in all capital letters. In this decision, the capitalization is eliminated without further notation.

[9] Plantar reflexes are "contraction of the toes when the sole of the foot is irritated; cf. Babinski r." Dorland's at 1614.

[10] Plasmapharesis is "the removal of plasma from withdrawn blood, with retransfusion of the formed elements of the donor . . . The procedure may be done for purposes of collecting plasma components or for therapeutic reasons." Dorland's at 1456.

Before the results from the MRIs were obtained, Dr. Garrett indicated that both GBS and transverse myelitis were possible diagnoses. He stated that the critical care team was working with Dr. Lake, the neurologist, and was implementing her orders. Id. at 136.

A series of MRIs was performed the following morning. The MRI for the brain was unremarkable. Exhibit 7 at 176. MRIs of Mr. Contreras's cervical, thoracic, and lumbar spine revealed an "extensive abnormal signal intensity noted in the cervical spinal cord. . . . The abnormality extends from the C2-3 interspace down to about C7. . . . Following gadolinium, there is no significant enhancement." The radiologist interpreting the image, Scott Lipson, stated that "[t]his appearance is not suggestive of Guillain-Barre syndrome and more likely represents an entity such as transverse myelitis." The results were discussed with Dr. Lake. Exhibit 7 at 167-71, 177-78.

Dr. Lake recorded information about the MRI when she saw Mr. Contreras at 1:45 PM on June 18, 2003. Dr. Lake stated that a "high signal [in the] cervical cord [was] [consistent with] transverse myelitis." Her impression was "? Transverse myelitis of cervical cord." She recommended completing the IVIG and starting solumedrol and prednisone.[11] Exhibit 7 at 1723.

In the afternoon of June 18, 2003, Dr. Babbitt dictated a progress note about Mr. Contreras's history of approximately 24 hours in the hospital. Dr. Babbitt reported that Mr. Contreras received a second dose of IVIG today and the neurology service started him on "solu-medrol / prednisone." Dr. Babbitt also stated that it was "unclear . . . whether he has transverse myelitis versus a [GBS] . . . type syndrome or even multiple sclerosis." Id. at 131.

Mr. Contreras was seen by Dr. Kimberly Bedell, who led his pediatric rehabilitation team throughout his lengthy hospitalization, on June 18, 2003. Exhibit 7 at 139-41. Her report is similar to Dr. Babbitt's report. Dr. Bedell recounted that the MRI of Mr. Contreras's cervical spine was "consistent with transverse myelitis. The patient will be completing IVIG treatments and will be started on intravenous steroids." Exhibit 7 at 139. In Dr. Bedell's review of symptoms, she recorded "Downgoing Babinski bilaterally." Id. at 140.

On June 19, 2003, Mr. Contreras had difficulty breathing and required "emergent intubation." Dr. Babbitt's report from this date also indicated that Mr. Contreras's disease "is now thought to be transverse myelitis." Id. at 129.

During the early portion of Mr. Contreras's hospitalization, his doctors referred to the shift in diagnosis. For example, on June 22, 2003, Dr. Babbitt stated Mr. Contreras "receive[d] two doses of IV IG when we were entertaining the diagnosis of atypical Guillain-Barre. Based on his markedly abnormal MRI, his diagnosis seems much more consistent with transverse myelitis." Id. at 123. Earlier, an infectious disease specialist, Dr. Michele Cheung, stated Mr.

[11] Prednisone is "derived from cortisone [and is] administered orally as an anti-inflammatory and immunosuppressant in a wide variety of disorders." Dorland's at 1509.

Contreras "received intravenous immunoglobulin for presumed Guillain-Barre syndrome, but then a repeat MRI scan at our facility showed abnormal signal in the cervical spine from about C2 through C7 and he was then given solu-medrol for a possible transverse myelitis." Id. at 145-47.

In the course of recording Mr. Contreras's history, Dr. Cheung noted that he had received his "third hepatitis-B vaccination and his tetanus booster on June 16, 2003." Mr. Contreras's parents were "very concerned that a vaccine may have caused this illness." Id. at 145. Dr. Cheung accepted that transverse myelitis was the appropriate diagnosis for Mr. Contreras and she noted "[i]t is often very difficult to find the exact cause of transverse myelitis, although many cases are preceded by upper respiratory or gastrointestinal symptoms." Dr. Cheung listed many possible antecedent infections but added that Mr. Contreras "has no other real exposures for any other types of infections." Id. at 147.

Dr. Cheung intended to address the parental concern about vaccinations. She reviewed the literature. She found no causal association. She explained:

> although there have been case reports associating hepatitis-B vaccine in particular (and also some with tetanus) with central nervous system problems and demyelinating diseases, there is no proof of causation and several cohort studies have suggested that there is no increased incidence following vaccination. In addition, the onset of [Mr. Contreras's] symptoms was quite rapid following the vaccination and other case reports have suggested a slightly longer latency prior to the actual onset of neurological symptoms.

Exhibit 7 at 147. Dr. Cheung concluded that she had "arranged an appointment with [Mr. Contreras's] parents . . . to discuss the infectious etiologies of transverse myelitis and the lack of evidence supporting a causal link with the hepatitis-B vaccine." Id.

Two days later, Dr. Babbitt commented upon the potential causative role of the vaccines. Dr. Babbitt stated that "[t]he family has been distraught over his underlying condition and the association of his problem with vaccines. We have tried to put them at ease, unfortunately we cannot tell them whether or not this was in fact caused by his hepatitis vaccine. There is no clear medical literature to support anything other than association. I have told the family this as has Dr. Lake and Dr. Ch[e]ung." Exhibit 7 at 126. The next day, Dr. Garrett stated "we will also make sure that the infectious disease service reports to the hepatitis B vaccination distributor the fact that the patient probably contracted or potentially contracted the transverse myelitis secondary to the hepatitis B vaccine." Id. at 106. After this point, although some doctors accurately stated that the vaccinations occurred before the onset of Mr. Contreras's neurological problems, see, e.g., exhibit 7 at 142, the doctors did not opine that the vaccinations caused the neurologic problem.

Following June 19, 2003, the doctors consistently identified Mr. Contreras's neurologic problem as transverse myelitis. Dr. Lake continued to see Mr. Contreras on an almost daily basis during his hospitalization and consistently considered him to be suffering from transverse

myelitis only. See, e.g., exhibit 7 at 16, 1554, 1612, 1627, 1633, 1676, 1698, 1711, 1712, 1714. Another neurologist, whose signature is illegible, considered Mr. Contreras to be suffering from transverse myelitis only. See exhibit 7 at 1694-95.

Dr. Garrett frequently stated Mr. Contreras suffered from transverse myelitis. See, e.g., exhibit 7 at 99, 101, 103, 107, 121. Furthermore, Mr. Contreras had numerous treating physicians during and after his hospitalization, many of whom saw him on an almost daily basis, who consistently opined—for months—that he suffered from transverse myelitis only. See, e.g., exhibit 7 at 177-78 (Dr. Scott Lipson, radiologist, on June 18, 2003), 123-24 (Dr. Babbitt on June 22, 2003), 142-44 (Dr. Sarah Sela-Herman, pediatric gastroenterologist, on June 30, 2003), 149 (Dr. Ayal Willner, otolaryngologist, on July 2, 2003), 219 (Dr. Nina Yoshpe, surgeon, July 3, 2003), 147 (Dr. Michele Cheung, infectious disease specialist, on July 7, 2003), 87-88 (Dr. Maria Elena Imperial on July 13, 2003), 115-16 (Dr. Graham Tse on July 16, 2003), 65-66 (Dr. Stephen Treiman on July 24, 2003), 61 ("team conference" on July 30, 2003 with, among others, Dr. Kimberly Bedell and Dr. Jennifer Davidson), 51 ("team conference" on August 20, 2003 with, among others, Dr. Bedell and Dr. Davidson), 154-56 (Dr. Richard Mathis, pediatric gastroenterologist, on August 25, 2003), 47-50 ("team conference" on September 3, 2003 with, among others, Dr. Kimberly Bedell and Dr. Jennifer Davidson).

Despite the apparent universal acceptance of the transverse myelitis diagnosis, the doctors at Miller Children's Hospital did not ever identify a cause of the transverse myelitis. They ordered many laboratory tests looking for evidence of an infectious agent. "[A]ll testing and evaluation for these specific causes," as Dr. Garrett later averred in his affidavit, "was unrevealing." Exhibit 13 at 7.

Mr. Contreras's condition worsened for approximately five days following his admission to Miller Children's Hospital. Among the problems he experienced were quadriplegia, acute respiratory failure, neurogenic bladder, acute cystitis, and priapism. Exhibit 13 ¶ 10; see also exhibit 7, passim, especially pages 6-8 (discharge summary).

Fortunately, Mr. Contreras improved. In early July 2003, he started to make some small movements with his hands and feet. He began to eat orally on July 17, 2003. He was transferred to a rehabilitation facility on July 30, 2003. He was discharged on September 11, 2003, and by that date, Mr. Contreras could feed himself finger foods, dress himself with some assistance, and walk 150 feet with a platform walker.

At Mr. Contreras's follow-up appointment in October 2003, Dr. Luis Montes recounted the change in diagnosis. Exhibit 80 at 31 ("initially the patient was felt to have [GBS] . . . [but] [a]s the symptoms progressed, the diagnosis was later changed to transverse myelitis."). He was hospitalized again for two weeks in November 2003 for inpatient rehabilitation. Again, his admission and discharge diagnoses were transverse myelitis. Exhibit 79 at 204-06.

Dr. Lake also examined Mr. Contreras during follow-up visits on November 2, 2004, February 1, 2005, and June 7, 2005. See exhibit 82 at 1-5. Her opinion from all three examinations was that Mr. Contreras suffered from transverse myelitis only. See id. at 1, 3, 5.

Mr. Contreras's treating physicians who cared for him well after his hospitalization also stated he suffered from transverse myelitis only. See, e.g., exhibit 80 at 10 (Dr. Luis Montes on Mar. 22, 2005), exhibit 95 at 47 (Dr. Jane Donat, neurologist, on August 17, 2006).

At the time of the hearing in Los Angeles, California, in 2010, Mr. Contreras described himself as having average health. He reported that he could walk, but not for long periods of time. Tr. 39; see also Opinion and Order, 107 Fed. Cl. at 285 (describing Mr. Contreras's condition at time of hearing).

III. Procedural History

There are two broad periods for the procedural history, separated by the April 5, 2012 Entitlement Decision. The more remote history is set forth to provide a context for the Court's September 28, 2012 Opinion and Order.

A. Events before the Court's Opinion and Order

There are four phases here: first, the early development of the case, second, the parties' submissions before the hearing and the hearing itself, third, the parties' post-hearing briefs, and fourth, the April 5, 2012 Entitlement Decision. Since many of these events were detailed in the April 5, 2012 Entitlement Decision and the Opinion and Order, 107 Fed. Cl. at 285-90, they are presented more summarily in the following sections.

1. Early Development

Mr. Contreras filed a petition[12] on June 15, 2005, in which he alleged that the hepatitis B and Td vaccines he received on June 16, 2003, caused him to develop transverse myelitis and GBS by June 17, 2003, approximately 24 hours after his vaccinations. Early submissions from Mr. Contreras included medical records, affidavits from Dr. Kyazze (exhibit 11), Dr. Wagner (exhibit 12), and Dr. Garrett (exhibit 13). Mr. Contreras also submitted two reports from Dr. Poser. Exhibits 22 and 23.

The Secretary filed her Rule 4 report on October 7, 2005, in which she indicated that Mr. Contreras was not entitled to compensation. The Secretary asserted that the evidence did not support a finding that either the Td or the hepatitis B vaccine can cause a demyelination condition, such as transverse myelitis or GBS. Resp't's Rep't at 9. The Secretary also asserted that, even if a vaccine could cause a demyelinating condition, it could not have done so within 24 hours of vaccination, as Mr. Contreras alleges occurred. Rather, the Secretary maintained that "a plausible interval between vaccination and the onset of symptoms is 5-45 days." Resp't's Rep't

[12] At the time the petition was filed, Mr. Contreras's parents represented him because he was a minor. The case caption was amended to designate Mr. Contreras as the sole petitioner because he had reached the age of majority. See Order, filed June 26, 2008. For ease of reference, this decision refers to Mr. Contreras as the petitioner.

at 9. The Secretary supported her position with the report of Dr. Sladky, a neurologist whom she had retained. Exhibit A.

The presiding special master appears to have sought evidence from Mr. Contreras showing that the timing in this case was medically appropriate. See Order, filed Nov. 18, 2005, at 2. In response to the special master's concern, Mr. Contreras obtained a report from another neurologist, Dr. Lawrence Steinman. Exhibit 55.[13] The parties explored settlement but did not succeed.

Because the parties' settlement discussions, including alternative dispute resolution with another special master, were unsuccessful, the Secretary filed expert reports in support of her position. The Secretary filed three expert reports from Dr. J. Lindsay Whitton, exhibits N, U, and BB, and a supplemental report from Dr. Sladky, exhibit O. Mr. Contreras also filed a supplemental report from Dr. Steinman. Exhibit 152.

2. Pre-Hearing Briefs and Hearing

Mr. Contreras submitted a pre-trial brief on March 8, 2010. Mr. Contreras alleged that he suffered from both transverse myelitis and GBS. Pet'r's Pre-trial Br., filed Mar. 8, 2010, at 6. Mr. Contreras indicated that Dr. Poser, Dr. Steinman, and the Secretary's expert, Dr. Whitton, all agreed with this dual diagnosis, but noted that the Secretary's other expert witness, Dr. Sladky, opined that the correct diagnosis was transverse myelitis. Id. at 6 n.7. Mr. Contreras did not anticipate the Secretary challenging his assertion that he suffered from both transverse myelitis and GBS despite Dr. Sladky's disagreement. Id. at 6.

Mr. Contreras asserted that both the hepatitis B and Td vaccines can cause demyelinating injuries, including transverse myelitis and GBS. Id. at 7. In support of this proposition, he noted that two of his treating physicians—Dr. Wagner and Dr. Garrett—opined that his condition was vaccine-related.[14] He also asserted that his two experts, Dr. Poser and Dr. Steinman, provided a reliable theory of causation. Id. at 8-10.[15] According to Dr. Poser and Dr. Steinman, the approximately 24-hour onset of Mr. Contreras's symptoms after vaccination is an acceptable time-frame due, in part, to Mr. Contreras's genetic makeup and his medical history, namely, his prior vaccinations. Id. at 12-13.

In her pre-trial brief, the Secretary asserted that Mr. Contreras had failed to present a reliable theory of causation. Specifically, the Secretary maintained that, regardless of which

[13] Mr. Contreras could not rely exclusively upon Dr. Poser because Dr. Poser's health prevented him from continuing in the litigation.

[14] As discussed in more detail below, Dr. Garrett diagnosed Mr. Contreras with only transverse myelitis, whereas Dr. Wagner diagnosed Mr. Contreras with atypical GBS and potential transverse myelitis.

[15] The opinions of Dr. Poser and Dr. Steinman are discussed in detail below.

disease afflicted Mr. Contreras, neither transverse myelitis nor GBS could have manifested within 24 hours after vaccination. The Secretary further questioned whether the hepatitis and/or the Td vaccines could cause demyelinating diseases, including transverse myelitis and GBS.

The parties filed an extensive amount of medical literature. Mr. Contreras attached an appendix to his pre-hearing brief that provided "short summaries of medical articles referenced by Dr. Steinman." Pet'r's Pre-hearing Br., App'x A, at 1.

At the hearing held on April 19-20, 2010, Dr. Kyazze, Dr. Wagner, and Dr. Steinman testified on behalf of petitioner. Dr. Garrett and Dr. Poser were unable to testify. Dr. Whitton and Dr. Sladky testified on behalf of respondent. At the hearing held by videoconference on July 28, 2011, Dr. Steinman testified on behalf of petitioner and Dr. Whitton testified on behalf of respondent.

3. Post-Hearing Briefs

The parties each submitted two post-hearing briefs. The parties disputed whether Mr. Contreras suffered from just transverse myelitis or both transverse myelitis and GBS. Mr. Contreras asserted that he suffered from both transverse myelitis and GBS. The Secretary maintained that the correct diagnosis was only transverse myelitis. However, the parties agreed, albeit for different reasons, that a determination of what afflicted Mr. Contreras was irrelevant to the outcome of this matter.

Mr. Contreras asserted that whether he suffered from transverse myelits or GBS or both "should not [a]ffect the outcome of the case since the testimony is that the cause of each disease was the vaccines administered." Pet'r's Post-Hearing Br., filed Aug. 23, 2010, at 15. The Secretary argued that "[w]hether [Mr. Contreras's] neurodemyelinating condition is TM or GBS does not change the fact that petitioner has failed to present a reliable medical theory that Hep B vaccine can cause either condition within 24 hours of administration." Resp't's Post-Hearing Br., at 5. Thus, according to Mr. Contreras, he asserted that he had satisfied all three Althen prongs regardless of what disease (or diseases) a preponderance of the evidence indicated afflicted him. Likewise, the Secretary argued that Mr. Contreras did not satisfy any of the Althen prongs even if he suffered from transverse myelitis and GBS.

Mr. Contreras also attached an appendix to his post-hearing brief that summarized the medical literature on which Dr. Garrett, Dr. Poser, and Dr. Steinman relied. Pet'r's Post-hearing Br., App'x A, at 1. Mr. Contreras indicated that these summaries were "written by lay individuals." Pet'r's Pre-hearing Br., App'x , at 57-80. (Although Mr. Contreras did not indicate that the summaries contained in the appendix to his post-hearing brief were written by lay individuals, the undersigned assumes that they were.) The undersigned agrees with Mr. Contreras that the summaries are "not a substitute for review of the article itself and expert opinion as to its content," id. at 1 n.1, and has reviewed the entirety of the record, but this decision focuses on the articles discussed most extensively by the experts in their testimony and the parties in their briefs.

4. Entitlement Decision

The Entitlement Decision found that a preponderance of the evidence supported a diagnosis of transverse myelitis, but not one of GBS. Before the Entitlement Decision, the parties did not consider a determination of which disease (or diseases) afflicted Mr. Contreras to be important. Mr. Contreras asserted that he had established entitlement to compensation either way, and the Secretary argued that neither GBS nor transverse myelitis could manifest in approximately 24 hours, as Mr. Contreras alleged.

The more important (and decisive) issue was whether Mr. Contreras had established that a vaccine can cause a demyelinating disease within one day. The Entitlement Decision found that Mr. Contreras did not meet his burden of proof on this issue. The Entitlement Decision found Dr. Steinman's tuberculin test analogy unpersuasive because it was "most importantly" based on a finding that "the tuberculin reaction occurs in an area not protected by the blood brain barrier" and a breach of the blood brain barrier would require much more than 24 hours. 2012 WL 1441315, at *19.[16] See Bazan v. Sec'y of Health & Human Servs., 539 F.3d 1347, 1352 (Fed. Cir. 2008) (discussing the need for a medically acceptable temporal relationship between vaccine and alleged injury). For that reason, Mr. Contreras's claim failed on Althen prong three and, consequently, he was not entitled to compensation. Entitlement Decision, at *1, *23-24.

B. Events after the April 5, 2012 Entitlement Decision

Following the April 5, 2012 Entitlement Decision, activities happened in three phases. The first phase was the motion for review. The second phase was the Court's Opinion and Order. The third phase consisted of the events taking place after the remand.

1. Mr. Contreras's Motion for Review and Associated Briefing

Mr. Contreras filed a motion for review of the Entitlement Decision with the Court on April 25, 2012. After a timely initial submission, Mr. Contreras submitted a lengthier motion that developed and expanded his arguments.

Mr. Contreras's amended motion, although organized differently, presented essentially three themes. First, Mr. Contreras challenged the finding that he suffered from transverse myelitis only and not transverse myelitis and GBS. Mr. Contreras argued that determining

[16] Although the Court found no error in that analysis, Opinion and Order, 107 Fed. Cl. at 305-06, it directed a reexamination of that finding, id. at 306 n.40, because the experts' testimony "regarding the blood brain barrier and the central nervous system . . . gains much greater importance if the diagnosis of GBS, a disease of the peripheral nervous system, is not applicable to [Mr. Contreras]." Id. at n.21. As discussed in section V.A below, a preponderance of the evidence indicates that Mr. Contreras suffered from transverse myelitis, not GBS. Accordingly, Dr. Steinman's tuberculin test analogy is not persuasive for the reasons discussed in the Entitlement Decision. 2012 WL 1441315, at *19.

whether he suffered from transverse myelitis and GBS was a significant issue because "the dual diagnosis . . . demonstrates the uniqueness of [Mr. Contreras]." Pet'r's Mot. for Review, filed May 4, 2012, at 20. Mr. Contreras pointed to aspects of his medical history that, in his view, support a finding that he suffered from GBS in addition to transverse myelitis. He noted that one of his treating physicians, Dr. Lake, diagnosed him with atypical GBS. Mot. for Rev., at 23 (citing exhibit 7 at 1735). Dr. Steinman interpreted the results of Mr. Contreras's Babinski reflex test to indicate the correct diagnosis was GBS. Dr. Steinman opined that the results of Mr. Contreras's spinal fluid examination were indicative of GBS. Mot. for Rev., at 21-22.

The second theme concerned the third prong of Althen, which Mr. Contreras recognized as "[t]he most contentious issue." Id. at 31. Mr. Contreras argued the undersigned failed to consider (or improperly assessed) evidence in the record pertaining to the issue of timing. Mr. Contreras cited to other decisions where special masters found the petitioner was entitled to compensation for demyelinating injuries that, according to Mr. Contreras, manifested within 72 hours after vaccination. Id. at 32-34. Mr. Contreras asserted these cases demonstrate that "in certain 'unique' individuals, demyelinating disease (involving the central nervous system) can occur . . . within twenty four (24) hours." Id. at 34. Mr. Contreras argued it was a mistake of law for the undersigned to consider legal authorities outside of the Vaccine Program that hold case reports hold little probative value for establishing causation. Id. at 36. Mr. Contreras also argued that the undersigned improperly assessed the value of the evidence concerning Dr. Steinman's tuberculin skin test analogy.

Further, Mr. Contreras also asserted the Entitlement Decision applied an unduly high burden of proof with regard to Althen prong three. Mr. Contreras argued this occurred, in part, due to the findings regarding the reliability of animal studies and the undersigned's interpretation of and reliance on other Program cases. Id. at 45-49. Mr. Contreras argued the Entitlement Decision applied an incorrect standard by "look[ing] for conclusive or persuasive proof in the medical literature" that would support Mr. Contreras's argument that transverse myelitis and GBS can manifest within 24 hours after vaccination. Id. at 41.

Additionally, Mr. Contreras asserted that his unique genetic makeup and immune system caused his body to respond to the vaccines differently than the general public might. Id. at 20. Mr. Contreras claimed that Hispanics, such as himself, respond differently to vaccines than do individuals from other ethnic backgrounds. Id. at 21. Mr. Contreras asserted that his Hispanic heritage, as well as his receiving multiple prior hepatitis B vaccines, affected (i.e., accelerated) the onset of his condition after his subject vaccination. Id. at 20, 24.

The third theme concerned the remaining two Althen prongs. Mr. Contreras asserted it was legal error to find an analysis of Althen prongs one and two unnecessary on the ground that he had failed to provide preponderant evidence with regard to Althen prong three. Id. at 39-40. Mr. Contreras also reiterated his assertion that he had satisfied these Althen prongs. He maintained that Dr. Steinman's proposed theory of molecular mimicry satisfied Althen prong one. Id. at 23-24. Likewise, Mr. Contreras asserted that he met his burden under Althen prong two through the testimony of his experts and treating physicians. Id. at 30.

The Secretary filed a response to Mr. Contreras's motion on June 4, 2012. The Secretary argued that the Entitlement Decision applied the correct standard with regard to all three Althen prongs. Resp't's Resp. at 6. The Secretary emphasized that evidence established that 24 hours after vaccination was an inappropriately short temporal interval for both transverse myelitis and GBS to manifest according to Mr. Contreras's proposed theory of molecular mimicry. Id. at 10

The Secretary noted that in his Motion for Review, Mr. Contreras "re-argued the same evidence that was considered in detail, and ultimately found unpersuasive." Id. at 2. Thus, the Secretary asserted that Mr. Contreras "has failed to demonstrate that the special master committed error[,] . . . rehashes interpretations of the evidence . . . and argues for a legal standard that is inconsistent with binding Federal Circuit precedent." Id. at 10. Simply stated, the Secretary argued that the Entitlement Decision properly weighed all relevant evidence and, in doing so, committed no legal error. Id. at 14.

Mr. Contreras filed a reply to the Secretary's response on June 25, 2012. In his reply, Mr. Contreras addressed the arguments made in the Secretary's response. He made a number of discrete objections to the Secretary's interpretations of the evidence, and criticized the Secretary's failing to discuss some of his arguments and evidence.

2. The Court's Opinion and Order

In its Opinion and Order, the Court discerned five "principal questions" that it had to resolve in its review of the Entitlement Decision. These questions are whether the undersigned

> was permitted to: (1) diagnose petitioner's illness before proceeding to an analysis of causation; (2) deny the petition without making findings on all three Althen prongs; (3) deny the petition without making a finding as to whether petitioner had ruled out alternative causes of his illness; (4) assign little weight to the opinions of treating physicians as to Althen prong three; and, (5) require a heightened level of proof as to a proximate temporal relationship between the vaccinations received and petitioner's illness.

107 Fed. Cl. at 282.

The Court held that "all but one of these questions must be answered in the negative." Id. The only question on which the Court gave a qualified positive response was the second, which asked whether Mr. Contreras's petition was properly denied based on a finding on one Althen prong. The Court held that it was permissible to deny compensation based on a finding that Mr. Contreras failed to establish one of the three Althen prongs. Id. at 295. Nevertheless, the Court stated it was "difficult" to determine if the undersigned had considered all evidence relevant to that prong. Id. Further, in the interest of judicial economy, the Court ordered the undersigned to make a finding on all three Althen prongs because the Court considers the case "to be a much closer call if evidence pertinent to all three Althen prongs is considered." Id. at 296.

The Court provided a "succinct outline of the legal framework [of the Court's opinion] for utilization by the [undersigned]" on remand. Opinion and Order, 107 Fed. Cl. at 308. This

outline contains six discrete directives with which the undersigned must comply on remand. See 42 U.S.C. § 300aa–12(e)(2)(c) (empowering the Court of Federal Claims to remand "to the special master for further action in accordance with the court's direction"); Hanlon v. Sec'y of Health & Human Servs., 40 Fed. Cl. 625, 630 (1998) (a decision from the Court of Federal Claims is binding on a special master in the same case on remand), aff'd on other grounds, 191 F.3d 1344 (Fed. Cir. 1999). On remand, the undersigned:

> 1. "may not diagnose [Mr. Contreras's] illness, but shall examine whether petitioner has established a prima facie case that he suffered a vaccine-related combination of TM and GBS"; 2. "shall make findings on all three Althen prongs"; 3. "shall make a finding as to whether petitioner has ruled out alternative causes for his illness"; 4. "shall accord the proper weight to the opinions of [Mr. Contreras's] treating physicians, as to all three Althen prongs"; 5. "shall employ the correct standard for Althen prong three"; and 6. "must consider Dr. Poser's arguments and evidence" concerning Althen prong three.

Opinion and Order, 107 Fed. Cl. at 308. The Court cautioned, however, that "[r]eference to this outline… is not a substitute for a thorough consideration and application of the legal analyses presented in [its] opinion." Id.

3. Activities on Remand

After the Court issued its Opinion and Order, a status conference was held on October 12, 2012. During the status conference, the parties requested additional time to discuss how to proceed with the case. See Order, filed October 15, 2012. On October 23, 2012, the parties filed a joint status report with a proposed briefing schedule. After being granted an extension of time to file his brief, Mr. Contreras filed his brief on remand on December 4, 2012. Pet'r's Br. on Remand, filed Dec. 4, 2012. The Secretary did not file her response to petitioner's brief on remand until June 12, 2013, after being granted multiple extensions of time to do so. Resp't's Br. on Remand. Mr. Contreras filed a reply brief on remand on August 13, 2013, after being granted an extension of time to do so.[17]

Mr. Contreras argued that he "erroneously agreed in [his] Post Trial Brief that whether [he] suffered from GBS or TM or a combination of the two diseases should not affect the outcome of the case." Pet'r's Br. on Remand at 7. Thus, his "focus on causation for GBS/TM without highlighting the difference in timing between GBS and TM was in retrospect an oversight." Id. Because his "experts and treating physicians have consistently maintained that Jessie suffered from both atypical GBS and TM," petitioner now urges a finding that he suffers from both GBS and transverse myelitis. Id.

The Secretary maintained her position that the diagnosis of Mr. Contreras's condition "does not change the fact that [Mr. Contreras] has failed to present a reliable medical theory that

[17] Although the Court expected the case to resolve quickly, Opinion and Order, 107 Fed. Cl. at 283, the parties sought enlargements of time to comply with the briefing schedule and to attempt (again) to resolve the case informally.

the Hep B or Td vaccine can cause either [TM or GBS] within 24 hours"[18] after vaccination. Resp't's Br. on Remand, at 10.

The remainder of the parties' arguments in their briefs on remand thoroughly explained their respective positions regarding the Court's five other directives. Simply stated, Mr. Contreras asserted that he has provided preponderant evidence to satisfy all three Althen prongs while the Secretary maintained that the record does not support a finding in his favor on any of the Althen prongs.

IV. Standards for Adjudication[19]

To receive compensation under the Program, Mr. Contreras must prove either: (1) that he suffered a "Table Injury"—i.e., an injury listed on the Vaccine Injury Table—corresponding to a vaccine that he received, or (2) that he suffered an injury that was actually caused by his hepatitis B or Td vaccination. See 42 U.S.C. §§ 300aa-13(a)(1)(A) and 11(c)(1); Capizzano v. Sec'y of Health & Human Servs., 440 F.3d 1317, 1319-20 (Fed. Cir. 2006). Here, Mr. Contreras is not claiming an injury listed on the Vaccine Table. Therefore, he must prove causation-in-fact.

When a petitioner proceeds on a causation-in-fact theory, a petitioner must establish three elements. The petitioner's

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

Althen, 418 F.3d at 1278.

In this passage, Althen indicates that petitioner's burden of proof is a preponderance of the evidence. Accord 42 U.S.C. § 300aa−13(a)(1). In this regard, "close calls regarding causation are resolved in favor of injured claimants." Althen, 418 F.3d at 1280.

The preponderance of the evidence standard, in turn, has been interpreted to mean that a fact is more likely than not. Moberly v. Sec'y of Health & Human Servs., 592 F.3d 1315, 1322

[18] As discussed in section V.C.2 below, the parties have a minimal (and unimportant) difference about the exact number of hours that elapsed between vaccination and the onset of neurological problems.

[19] The Court also discussed how a petitioner may establish a causation-in-fact claim. Opinion and Order, 107 Fed. Cl. at 291-92.

n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991).

Distinguishing between "preponderant evidence" and "medical certainty" is important because a special master should not impose an evidentiary burden that is too high. Andreu v. Sec'y of Health & Human Servs., 569 F.3d 1367, 1379-80 (Fed. Cir. 2009) (reversing judgment that petitioners were not entitled to compensation); see also Lampe v. Sec'y of Health & Human Servs., 219 F.3d 1357 (2000); Hodges v. Sec'y of Health & Human Servs., 9 F.3d 958, 961 (Fed. Cir. 1993) (disagreeing with dissenting judge's contention that the special master confused preponderance of the evidence with medical certainty).

The obligation in determining whether the evidence weighs in petitioner's favor rests with special masters in the first instance. 42 U.S.C. § 300aa−12(d)(3)(A). "Congress envisioned that the special masters would become specialists in vaccine-related injuries and would use 'their accumulated expertise in the field [to] judg[e] the merits of the individual claims.'" Simanski v. Sec'y of Health & Human Servs., 671 F.3d 1368, 1371 (Fed. Cir. 2012) (quoting Lampe, 219 F.3d at 1362 (citations omitted)).[20]

Mr. Contreras argues he has provided preponderant evidence to meet his burden under Althen to prove his TM and GBS were caused in fact by the hepatitis B and/or Td vaccine.[21] An evaluation of each prong follows.

V. Analysis

Four aspects of this case are determined. The preliminary question (section V.A.) is whether Mr. Contreras suffered from either transverse myelitis alone or transverse myelitis and GBS. The next three sections correspond to the three prongs of Althen. Section V.B. discusses Mr. Contreras's submission of a medical theory that causally connects the hepatitis B vaccination to his neurological injury. Section V.C. explains whether Mr. Contreras has presented preponderant evidence that this theory explains how a vaccine can cause a neurologic

[20] After a motion for review, if the Court finds that the special master's findings of facts were "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance of law," the Court may "issue its own findings of fact." 42 U.S.C. § 300aa−12(e)(2)(B); accord Porter v. Sec'y of Health & Human Servs., 663 F.3d 1242, 1249 (Fed. Cir. 2011). In its Opinion and Order, the Court did not make any findings of fact. Opinion and Order, 107 Fed. Cl. at 292. Instead, the Court remanded the case "for further action in accordance with the court's direction." See 42 U.S.C. § 300aa−12(e)(2)(C).

[21] Dr. Steinman opined that Mr. Contreras's hepatitis B vaccination caused his condition, but also suggested that his Td vaccination could have contributed to it. He explained at the hearing, however, that "without the hepatitis B vaccine, we would not be in court today." Tr. 118.

injury within a medically acceptable amount of time. The final section discusses whether Mr. Contreras has presented a logical sequence of cause and effect connecting his vaccination and his injury.

A. Mr. Contreras's Injury

Mr. Contreras contends his vaccines caused him to develop both transverse myelitis and GBS. The Secretary's position regarding what injury (or injuries) afflicts Mr. Contreras is not entirely clear or consistent. The Secretary has, however, clearly and consistently maintained her position that the exact diagnosis of Mr. Contreras's condition is unimportant because he could not have developed either transverse myelitis or GBS within approximately 24 hours after vaccination.

The evidence concerning Mr. Contreras's diagnosis comes from three sources. The first and most important source is the material coming from Mr. Contreras's treating doctors. The next source is the set of opinions from doctors whom Mr. Contreras has retained. The final source is the set of opinions from doctors whom the Secretary retained. After the summaries of this material, there is a determination about how the evidence preponderates.

By weighing the evidence, the undersigned has attempted to comply with the Court's instruction not to diagnose Mr. Contreras's illness. 107 Fed. Cl. at 308. As discussed in more detail below, the doctors have diagnosed him.

1. Position of Doctors who Treated Mr. Contreras

A chronological presentation of the treating doctors' diagnoses begins with Dr. Wagner. Dr. Wagner treated Mr. Contreras on his admission to the emergency room on June 17, 2003. Upon Mr. Contreras's admission, Dr. Wagner diagnosed him with atypical GBS. Exhibit 6 at 5; Tr. 73. Dr. Wagner also considered a diagnosis of transverse myelitis. Tr. 82-83. When Dr. Wagner transferred Mr. Contreras to Miller's Children Hospital, Dr. Wagner's diagnosis was atypical GBS. Exhibit 6 at 5.

Although Mr. Contreras did not see Dr. Wagner after Dr. Wagner transferred Mr. Contreras, Tr. 91, Mr. Contreras, acting through his attorney, consulted Dr. Wagner. Dr. Wagner's affidavit stated that his "clinical impression [of Mr. Contreras] was atypical [GBS]" and that his "differential diagnosis was Early Transverse Myelitis." Exhibit 12, ¶ 5. At the hearing, Dr. Wagner testified that Mr. Contreras suffered from both transverse myelitis and GBS. The basis for Dr. Wagner's opinion concerning a dual diagnosis was primarily his extensive clinical experience. Tr. 94-95.

The next doctor to reach an opinion regarding Mr. Contreras's diagnoses was Dr. Lake. Dr. Lake saw Mr. Contreras within hours of his admission to Miller's Children Hospital. Although Dr. Lake initially considered a diagnosis of atypical GBS upon Mr. Contreras's admission, exhibit 7 at 1735, she changed her diagnosis to transverse myelitis due to the results of his June 18, 2003 MRI. Dr. Lake (and Mr. Contreras's radiologist, Dr. Lipson) considered the results to suggest transverse myelitis, not GBS. Exhibit 7 at 177, 1723. Dr. Lake was Mr.

Contreras's primary neurologist and, after the June 18, 2003 MRI, she consistently opined that Mr. Contreras had only transverse myelitis during his three-month hospitalization. Her opinion was the same in three consecutive follow-up examinations on November 2, 2004, February 1, 2005, and June 7, 2005. See exhibit 82 at 1-5.

The next important doctor to comment upon Mr. Contreras's diagnosis was Dr. Garrett. Dr. Garrett's initial differential diagnosis included atypical GBS, transverse myelitis, acute disseminated encephalomyelitis, and multiple sclerosis. Exhibit 7 at 136; see also exhibit 13 at 6. However, Dr. Garrett conferred with Dr. Lake and seemingly deferred to Dr. Lake's opinion that Mr. Contreras had transverse myelitis. See exhibit 7 at 136. After Dr. Lake stated that Mr. Contreras had transverse myelitis, Dr. Garrett's reports consistently mention only transverse myelitis. None of his reports after June 18, 2003 mentions GBS.

The affidavit that Mr. Contreras procured from Dr. Garrett is consistent with this characterization. Dr. Garrett averred that Mr. Contreras's initial workup included treatment for GBS. But, his final diagnosis was transverse myelitis. Exhibit 13 at 7.

The final doctor who treated Mr. Contreras and presented an opinion for this litigation was Dr. Kyazze. Dr. Kyazze performed a physical checkup on Mr. Contreras the day before his vaccinations. Tr. 12. Dr. Kyazze learned from personnel at Miller Children's Hospital that Mr. Contreras was hospitalized for transverse myelitis. Exhibit 11 at 2, ¶ 7; Tr. 60. On June 23, 2003, Dr. Kyazze completed a VAERS report in which he indicated that Mr. Contreras had been "hospitalized in ICU for transverse myelitis on 6/17/03." Exhibit 4 at 44; Tr. 55-56. When he testified, Dr. Kyazze did not comment on whether transverse myelitis or GBS was the correct diagnosis for Mr. Contreras's condition. See Tr. 59-60.

Additionally, many other doctors saw Mr. Contreras during his hospitalization. Although they did not testify, their reports are part of the record. These doctors consistently indicated that he suffered from only transverse myelitis. Whether these doctors determined this diagnosis independently or whether they deferred to the opinion of Mr. Contreras's treating neurologist, Dr. Lake, is not clear. Regardless, none of them suggested GBS.

2. Position of Mr. Contreras

a) Dr. Poser

Dr. Poser opined that Mr. Contreras suffered from both transverse myelitis and GBS. See exhibit 23 at 7, ¶ 15. In his view, the signs and symptoms of transverse myelitis "masked" those of GBS. Exhibit 22 at 3, ¶ 4. Dr. Poser acknowledged that "[t]he original diagnosis of [GBS] . . . was then changed to cervical transverse myelitis as a result of a second MRI . . . on June 18, 2003," exhibit 22 at 2, ¶ 3, but he opined that "[f]rom the clinical examination and the MRI, it is clear that [Mr. Contreras] suffered from a combination of [GBS] . . . and . . . transverse myelitis." Exhibit 22 at 3, ¶ 4. Although Dr. Poser recounted his understanding of Mr. Contreras's clinical presentation and the results of his June 18, 2003 MRI, see exhibit 22 at 2, ¶ 3, Dr. Poser did not explain how the June 18, 2003 MRI is consistent with GBS. Dr. Poser

also did not explain why the results of the June 18, 2003 MRI did not explain the basis for Mr. Contreras's clinical symptoms.

b) Dr. Steinman

In his report, Dr. Steinman stated Mr. Contreras "developed transverse myelitis and an inflammatory peripheral neuropathy, commonly known as Guillain Barre syndrome." Exhibit 55 at 1. Dr. Steinman agreed with the opinions of Mr. Contreras's treating physicians, who diagnosed him with transverse myelitis. In Dr. Steinman's opinion, "a secondary diagnosis of inflammatory polyradiculopathy/polyneuropathy [Guillain-Barré Syndrome] could also be made." Exhibit 55 at 2 (bracketed material in original).

In his testimony, Dr. Steinman opined that Mr. Contreras exhibited "elements of both transverse myelitis and [GBS]." Tr. 118. For that reason, he did not consider it "possible to say [Mr. Contreras] had only one or only the other" of the two diagnoses, Tr. 119, because his clinical history "doesn't fit perfectly into either [diagnosis]." Tr. 186.

Dr. Steinman explained that transverse myelitis and GBS can have both similar and dissimilar initial presentations. Tr. 182. Dr. Steinman considered a diagnosis of GBS due to Mr. Contreras's Babinski reflexes, the absence of lymphocytes in his cerebrospinal fluid, and the diagnoses of his treating physicians. Tr. 121-22, 183-87. Dr. Steinman considered that a dual diagnosis was a possibility because Mr. Contreras received effective treatment for his GBS during his hospitalization and the GBS had apparently subsided. See Tr. 185, 213.

Dr. Steinman acknowledged that when Dr. Garrett discharged Mr. Contreras on September 11, 2003, Dr. Garrett diagnosed him with transverse myelitis, not GBS. Tr. 186. In developing his opinion on Mr. Contreras's diagnosis, this specificity did not "concern [Dr. Steinman] as much as it might concern others" because Dr. Steinman did not attribute much weight to Dr. Garrett's discharge diagnosis. Tr. 186; exhibit 7 at 6. Dr. Steinman appeared to suggest that the discharge diagnosis did not include GBS because hospital personnel, presumably including Dr. Lake and Dr. Garrett, "may have lost sight of the early nuances in the case." Tr. 186.

c) Counsel's Arguments

Mr. Contreras has consistently maintained that he suffered from both transverse myelitis and GBS. In support, Mr. Contreras pointed to Dr. Wagner's, Dr. Garrett's, and Dr. Poser's diagnoses, as well as that of the Secretary's expert, Dr. Whitton. See, e.g., Pet'r's Br. on Remand at 8-12; Pet'r's Post-Hearing Br. at 13.

3. Position of the Secretary

a) Dr. Sladky

Dr. Sladky opined that Mr. Contreras had transverse myelitis only. He explained that he "found nothing in the medical records . . . to suggest or substantiate a dual diagnosis [of

transverse myelitis and GBS]." Exhibit I at 3. He stated that approximately 2-5% of patients suffer from both transverse myelitis and GBS concurrently. Tr. 293.

Dr. Sladky indicated that the results of the Babinski test did not mean that Mr. Contreras had GBS. Dr. Sladky also considered Mr. Contreras's back pain, arm weakness, and diminished reflexes to be consistent with transverse myelitis. Tr. 283-84. He attributed Mr. Contreras's complications in his hands and legs, which may indicate GBS, to be due to inflammation in the cervical cord. Tr. 287-88.

b) Dr. Whitton

Dr. Whitton testified that when the Secretary retained him in this litigation, he understood that his role "was to evaluate the immunology and the timing of the immunology . . . rather than the neurology." Tr. 438. As such, Dr. Whitton did not consider it important to determine the correct diagnosis for Mr. Contreras's condition.

In Dr. Whitton's first report, he opined that Mr. Contreras suffered from both GBS and TM. Exhibit L at 3. He testified that "[f]rankly, my opinions expressed in my first report [regarding Mr. Contreras's diagnosis] were based largely on reading the expert reports of Dr. Poser and Dr. Steinman." Tr. 438.

On further review, Dr. Whitton opined that Mr. Contreras's medical records "may indicate that the treating physicians considered his clinical picture more typical of transverse myelitis than of GBS." Exhibit N at 5. Specifically, Dr. Whitton stated that Mr. Contreras's "discharge diagnosis and the treatment he received (and did not receive)" were more suggestive of transverse myelitis than GBS. Exhibit N at 5 (citing exhibit 7 at 35 (documenting intravenous steroid and IVIG treatment)), 113 (documenting that Mr. Contreras did not receive plasmapheresis[22] treatment)).

At the hearing, when pressed to opine about whether Mr. Contreras suffered from GBS, Dr. Whitton testified that whether Mr. Contreras suffered from transverse myelitis or GBS did not affect his opinion because neither could manifest within 24 hours after his vaccinations. See Tr. 438. He also considered the question of diagnosis to be outside of his expertise. See Tr. 438, 454-55.

c) Counsel's Arguments

The Secretary's pre-hearing brief is not a model of clarity regarding the appropriate diagnosis for Mr. Contreras. See Opinion and Order, 107 Fed. Cl. at 287 n. 18. Initially, she framed the issue of this case as "whether the administration of a Hepatitis B . . . vaccine and tetanus-diphtheria booster . . . on June 16, 2003, caused in fact Jessie Contreras's Transverse Myelitis" within 24 hours. Resp't's Prehearing Br. at 1. The reference to transverse myelitis

[22] See supra page 12 n.10.

implies that the Secretary viewed transverse myelitis as the only diagnosis for Mr. Contreras. But, under a later section outlining Mr. Contreras's purported burden of proof, the Secretary points out that "[n]either GBS or TM are injuries listed in [the] Vaccine Table . . . for the Hep B and Td vaccine." Id. at 5. In discussing her stance on the reliability of Mr. Contreras's experts' medical theories of causation, the Secretary first concedes that a vaccine "might cause a neurodemyelinating disease such as TM or GBS." Id. at 23. These references to transverse myelitis and GBS suggest that GBS is an appropriate diagnosis for Mr. Contreras. The Secretary also stated that Dr. Kyazze, Dr. Wagner, and Dr. Garrett all opined that Mr. Contreras had transverse myelitis; the Secretary did not address whether they believed he also suffered from GBS. See id. at 26.

In the Secretary's post-hearing brief, she acknowledged Mr. Contreras's position that his vaccines caused him to develop both transverse myelitis and GBS. Resp't's Post Hearing Br., at 1. Dr. Whitton initially agreed with Mr. Contreras's experts that he had both TM and GBS. The Secretary notes that Dr. Sladky questioned whether Mr. Contreras had GBS, but ultimately concluded that whether he had transverse myelitis or GBS, or both, did not change his opinion that Mr. Contreras's condition was not vaccine-related. Id. at 4. Even though the Secretary's experts arguably disagreed on Mr. Contreras's exact diagnosis, they both unequivocally agreed that "there was no biologically plausible mechanism by which [the] Hep B vaccine could cause a neurodemyelinating process within 24 hours of administration." Id. at 5.

On remand, the Secretary's position has not changed. In her brief on remand, the Secretary maintains her position that determining whether Mr. Contreras developed transverse myelitis or GBS, or both, "does not change the fact that petitioner has failed to present a reliable medical theory that the Hep B or Td vaccine can cause either condition within 24 hours" after vaccination. Resp't's Br. on Remand, at 10. The Secretary therefore does not necessarily disagree with Mr. Contreras's position that he suffered from both transverse myelitis and GBS. Rather, the Secretary considers the resolution of that issue unimportant because Mr. Contreras's claim will fail on other grounds regardless of whether the undersigned finds that he suffered from transverse myelitis alone or both transverse myelitis and GBS.

4. Determination

Everyone agrees that Mr. Contreras had transverse myelitis. The only dispute is whether he also had GBS. The evidence about whether Mr. Contreras had GBS is in conflict. Dr. Steinman, Dr. Poser, and Dr. Wagner opined that Mr. Contreras had both transverse myelitis and GBS. Dr. Whitton's opinion on Mr. Contreras's diagnosis was equivocal. In contrast, Dr. Garrett, Dr. Sladky, and a number of Mr. Contreras's treating physicians, including his primary neurologist, Dr. Lake, opined that he had only transverse myelitis. When evidence is in conflict, a special master's role is to weigh the evidence. See Moberly, 592 F.3d at 1325 (special masters have the responsibility to "assess the reliability of testimony, including expert testimony").

The opinions of treating physicians are entitled to substantial weight. Capizzano, 440 F.3d at 1326; Opinion and Order, 107 Fed. Cl. at 299 n.31. Dr. Garrett consulted with Dr. Lake to assess Mr. Contreras's neurological condition. Although at intake Dr. Lake stated that he had "atypical GBS," she changed her diagnosis to transverse myelitis due to the results of Mr.

Contreras's June 18, 2003 MRI. Dr. Lake saw Mr. Contreras on an almost daily basis during his three-month hospitalization. She saw him multiple times in follow-up examinations in the months afterward. After all of these visits, Dr. Lake's diagnosis was transverse myelitis.[23] As Mr. Contreras's primary neurologist for months, her opinion on the issue of Mr. Contreras's diagnosis is highly persuasive.

As discussed, Dr. Garrett was involved with Mr. Contreras's treatment during his hospitalization from June 17, 2003 through September 11, 2003. Exhibit 13 at 2-4. Dr. Garrett "was involved in the acute management and diagnostic workup of [Mr. Contreras's] presenting illness." Id. at 3. Dr. Garrett's initial differential diagnosis on Mr. Contreras's presentation "included . . . Transverse Myelitis, atypical Guillain-Barre syndrome, ADEM . . . or possibly new onset multiple sclerosis." Id. at 6. On July 20, 2013, Dr. Garrett stated that Mr. Contreras "probably . . . or potentially contracted the transverse myelitis secondary to the Hepatitis B vaccine." Id. at 6. Mr. Contreras's discharge diagnosis was cervical transverse myelitis. Id. at 4. Dr. Garrett's ultimate opinion was that it was "more likely than not that the vaccine was a *substantial factor* in causing or significantly contributing to [Mr. Contreras's] development of cervical transverse myelitis." Id. at 13 (emphasis in original).

Dr. Garrett is the only doctor to testify who was substantially involved in Mr. Contreras's care. He observed and treated Mr. Contreras during the entirety of his approximately three-month hospitalization, and stated Mr. Contreras suffered from only transverse myelitis on many occasions. See, e.g., exhibit 7 at 99, 101, 103, 107, 121. As a treating physician who was heavily involved in Mr. Contreras's treatment during the critical time of Mr. Contreras's hospitalization, his diagnosis of transverse myelitis is the most persuasive of the testifying witnesses.

To counter Dr. Garrett's diagnosis (as well as the diagnoses of numerous other treating physicians, including Dr. Lake), Mr. Contreras relies upon two doctors who never treated him, Dr. Steinman and Dr. Poser. Their opinions, although respectfully offered, are not persuasive. Accordingly, a preponderance of the evidence supports a finding that transverse myelitis is the sole diagnosis.[24]

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[23] Mr. Contreras contended that Dr. Lake diagnosed him with GBS. See Pet'r's Br. on Remand at 9 (citing exhibit 7 at 1735, Dr. Lake's June 17, 2003 diagnosis). Dr. Lake made this report on the first day of Mr. Contreras's hospitalization when the only information about the cervical MRI was negative. See exhibit 7 at 1735. Dr. Lake indicated Mr. Contreras's condition was "probable atypical [GBS]." Exhibit 7 at 1728, 1735.

By June 20, 2003, Dr. Lake changed the diagnosis from atypical GBS to transverse myelitis because of the MRI results from the second day of his hospitalization. See id. at 1714, 1723. Thus, although Mr. Contreras's argument regarding Dr. Lake has minimal support, the balance of Dr. Lake's treatment notes are inconsistent with Mr. Contreras's argument. See 42 U.S.C. § 300aa-13(a)(1) (a special master is charged with considering the "record as a whole").

[24] The Court indicated that the undersigned special master "may not diagnose Jessie's illness." Opinion and Order, 107 Fed. Cl. at 308. The finding that Mr. Contreras did not suffer

(... continued)

It bears repeating that there is no dispute that Mr. Contreras suffered from transverse myelitis. Even Mr. Contreras's experts agreed with Dr. Lake's diagnosis of transverse myelitis. Exhibit 22 at 2, ¶ 3; exhibit 23 at 7, ¶ 15 (Dr. Poser); exhibit 55 at 2 (Dr. Steinman). The diagnosis of transverse myelitis is practically inescapable because the June 18, 2003 MRI showed "extensive abnormal signal intensity . . . in the cervical spinal cord, . . . extend[ing] from the C2-3 interspace to about C7." Exhibit 7 at 167. This damage was to the central nervous system, which is usually protected by the blood brain-barrier. Tr. 226, 305-06, 418.

The April 5, 2012 Entitlement Decision emphasized that the blood brain barrier would make an autoimmune-mediated injury very unlikely to happen in one day. 2012 WL 1441315, at *14, *19. The Court expressed concern about the emphasis on the injury within the central nervous system. Opinion and Order, 107 Fed. Cl. at 289 n. 22. The reason for the emphasis on transverse myelitis (and the blood-brain barrier, which protects against transverse myelitis) is that Mr. Contreras unquestionably suffered from transverse myelitis. His theory of causation must necessarily take into account the lesion in his cervical spine that extended across four vertebrae. See Broekelschen v. Sec'y of Health & Human Servs., 618 F.3d 1339, 1345 (Fed. Cir. 2010) ("[A] petitioner must provide a reputable medical or scientific explanation that pertains specifically to the petitioner's case.").

According to Mr. Contreras, a determination that he also suffered from GBS "drastically undercuts" the Secretary's position with regard to Althen prong three because the Secretary's "principal argument" is that "the blood brain barrier can not be breached within 24 hours… [in] central nervous system diseases, not to peripheral nervous system diseases such as GBS where the blood brain barrier is not applicable." Pet'r's Br. on Remand at 49. This argument misses its mark. Mr. Contreras's argument might have more appeal if this were a case in which the debate was over whether the injury was either to the central nervous system or to the peripheral nervous system. If a person suffered an injury that was exclusively to the peripheral nervous system, then it seems an autoimmune process could occur more quickly simply because the strong defense offered by the blood brain barrier would not be an impediment. But, that is not the case with Mr. Contreras. He claims to have suffered both a disease of the central nervous system (transverse myelitis) and a disease of the peripheral nervous system (GBS). Thus, even if preponderant evidence established that Mr. Contreras suffered from both a peripheral and a central nervous system disease, he would be required to establish, on a more likely than not basis, that a

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GBS appears to be in accord with this instruction because Dr. Lake (not the undersigned) diagnosed Mr. Contreras's illness. Rather than diagnosing the illness, the undersigned has weighed all the evidence of record, including Dr. Steinman's and Dr. Poser's opinions, and determined that the stronger and more persuasive evidence supports a finding that Mr. Contreras suffered from transverse myelitis only. See Whitecotton v. Sec'y of Health & Human Servs., 81 F.3d 1099, 1108 (Fed. Cir. 1996) ("Congress desired the special masters to have very wide discretion with respect to the evidence they would consider and the weight to be assigned that evidence.").

vaccination caused both. And part of Mr. Contreras's case would include a showing that his injuries (GBS and transverse myelitis) arose in "a medically-acceptable time-frame." Opinion and Order, 107 Fed. Cl. at 309. Therefore, the medically-acceptable time-frame for the onset of transverse myelitis after vaccination would remain an issue even if Mr. Contreras were found to suffer from GBS in addition to transverse myelitis.[25]

This discussion about the significance of a finding that Mr. Contreras also suffered from GBS is purely hypothetical. His treating neurologist (Dr. Lake) and his treating pediatric intensivist (Dr. Garrett) concluded that Mr. Contreras suffered only from transverse myelitis. As treating doctors, their identification of the disease afflicting their patient is entitled to "significant weight." See Opinion and Order, 107 Fed. Cl. at 300.

Therefore, the remainder of this opinion discusses transverse myelitis. Mr. Contreras initially asserted that both his hepatitis B and Td vaccines caused his injuries. His experts, however, consistently attributed his injuries to only the hepatitis B vaccine, not the Td vaccine. Thus, the following Althen analysis is limited to the issue of whether the hepatitis B vaccine can cause transverse myelitis.[26]

B. Prong One from Althen – Medical Theory

After a determination of what disease afflicts a petitioner, the next step is analyzing the theory proposed by the expert that "causally connect[s] the vaccination and the injury." Althen, 418 F.3d at 1278. This element of petitioner's case is sometimes referred to as answering the "can it" question. Pafford v. Sec'y of Health & Human Servs., No. 01-165V, 2004 WL 1717359, at *4, 9 (Fed. Cl. Spec. Mstr. July 16, 2004), mot. for rev. denied, 64 Fed. Cl. 19 (2005), aff'd, 451 F.3d 1352 (Fed. Cir. 2006).

[25] In light of the undisputed results from the MRI showing demyelination in Mr. Contreras's cervical spine, exhibit 7 at 177, Mr. Contreras's attempt to add GBS to his case actually makes his claim more complicated. Under his theory, he would be required to show that his immune system directed itself against two different parts of his body, the central nervous system (cervical spine) and a portion of the peripheral nervous system. This autoimmune attack would also have to been initiated and to have caused some neurologic symptoms attributable to both central nervous system and peripheral nervous system in approximately one day.

[26] In spite of the fact that preponderant evidence supports a finding that Mr. Contreras suffered from only transverse myelitis, the undersigned has reviewed the entirety of the record to ensure that all relevant evidence has been considered. This review included the parties' medical literature that pertains to GBS and the Td vaccine. Although all the evidence has been considered, not all of it will be discussed in this decision. See Paterek v. Sec'y of Health & Human Servs., ___ F.3d ___, No. 2012-5078, 2013 WL 3028726, at *8 (Fed. Cir. June 19, 2013) (stating that "[f]inding certain information not relevant does not lead to—and likely undermines—the conclusion that it was not considered").

In the Vaccine Program, an expert's opinion may be evaluated according to the factors identified by the United States Supreme Court in Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579 (1993). Terran v. Sec'y of Health & Human Servs., 195 F.3d 1302, 1316 (Fed. Cir. 1999). After Terran, decisions from judges of the Court of Federal Claims have consistently cited to Daubert. E.g., Caves v. Sec'y of Health & Human Servs., 100 Fed. Cl. 119, 133 (2011), aff'd, 463 Fed. App'x 932 (Fed. Cir. 2012) (per curiam). Although supporting medical literature is not necessary for an expert's testimony to be reliable, Althen, 418 F.3d at 1279-80, Andreu, 569 F.3d at 1378, it may be considered in assessing the reliability of an expert's testimony.

The April 5, 2012 Entitlement Decision did not address Mr. Contreras's medical theory because his failure to present preponderant evidence on prong three meant that he was not entitled to compensation. 2012 WL 1441315, at *1. Although the Court held that the omission of prong one did not constitute an error of law, Opinion and Order, 107 Fed. Cl. at 295, the Court also instructed that the decision on remand discuss each of the Althen prongs. Id. at 296. In accord with the Court's direction, the evidence related to this prong is reviewed, starting with Mr. Contreras's evidence.

1. Synopsis of Mr. Contreras's Evidence

Mr. Contreras elicited testimony from five doctors regarding the cause of his disease. This group includes three doctors who treated him (Dr. Kyaaze, Dr. Wagner, Dr. Garrett) and two doctors who did not treat him (Dr. Poser and Dr. Steinman). Of this group, the doctor on whom Mr. Contreras relied most heavily was Dr. Steinman. See, e.g., Pet'r's Pre-Hearing Br. at 12; Pet'r's Post-Hearing Br. at 19, 21-22, 26; Pet'r's Mot. for Rev. at 9, 27-28, 29-30.

a) Dr. Kyazze

Mr. Contreras offered the affidavit of Dr. Kyazze to demonstrate that he was "a healthy individual with no infectious disease process taking place" prior to his vaccinations. Pet'r's Br. on Remand, at 13. Dr. Kyazze examined Mr. Contreras on June 16, 2003, prior to his subject vaccines. Exhibit 11 at 2; Tr. 54-55. He did not treat Mr. Contreras any time after June 17, 2013. Tr. 59. He has not reviewed any of Mr. Contreras's medical records since he administered Mr. Contreras's June 16, 2003 vaccinations. Tr. 59. As Mr. Contreras asserted, Dr. Kyazze considered Mr. Contreras to be entirely healthy prior to his vaccinations. Exhibit 11 at 2, ¶ 4.

On Mr. Contreras's emergency room admission, Dr. Kyazze was informed that Mr. Contreras had transverse myelitis. Tr. 59; see also exhibit 4 at 22. After learning that Mr. Contreras was in the intensive care unit for his transverse myelitis, Dr. Kyazze filed a Vaccine Adverse Event Report concerning Mr. Contreras. Exhibit 11 at 2, ¶ 7; Tr. 55, 60. He believed he was required by law to file a VAERS report because Mr. Contreras "developed serious symptoms within one day of receiving the vaccinations." Exhibit 11 at 2, ¶ 7; Tr. 56-57, 60. When asked whether he believed Mr. Contreras's vaccines caused his transverse myelitis, Dr. Kyazze stated he "wouldn't know that." Tr. 60. Beyond filing a VAERS report, Dr. Kyazze has not suggested that Mr. Contreras's transverse myelitis is vaccine-related.

b) Dr. Wagner

Dr. Wagner treated Mr. Contreras for approximately five hours of his first emergency room admission on June 17, 2008. Exhibit 12 at 2; exhibit 6 at 9; Tr. 66-69.

Dr. Wagner's clinical impression of Mr. Contreras upon his admission was atypical GBS. Exhibit 6 at 5, 10; Tr. 73, 84. Dr. Wagner's differential diagnosis of Mr. Contreras included transverse myelitis. Exhibit 12 at 2, ¶ 5; see also exhibit 6 at 18 (Dr. Wagner ordered an MRI due to "[c]onsideration of transverse myelitis"). Because Mr. Contreras developed his transverse myelitis shortly after his immunizations, Dr. Wagner considered them "a suspected cause." Exhibit 12 at 2, ¶ 6. Further, he "was not able to find any other reason or condition based on the medical history and upon my examination of [Mr. Contreras] which could have caused his reaction." Id.

In his affidavit, Dr. Wagner did not provide a theory of causation, nor did he expand on his opinion that Mr. Contreras's transverse myelitis is vaccine-related. At the hearing, Dr. Wagner offered additional information. He stated that "[a]fter discussing with Dr. Babbitt . . . [he] was of the understanding that the most likely possibility at the time was the hepatitis B [vaccine]." Tr. 89. In Dr. Wagner's view, "science has shown, and on [his] subsequent readings after the fact, that there are proteins in [the] hepatitis B vaccine that mimic myelin proteins around the nerves of human beings. And therefore, you can get an immune reaction," which can occur in 24 hours. Tr. 95-96. The readings to which Dr. Wagner referred are Dr. Steinman's report and references. Tr. 98.

Dr. Wagner based his testimony upon a review of his treatment records, Dr. Garrett's report, and Dr. Steinman's report and references. Tr. 92, 97-98. Dr. Wagner did not review the reports of Dr. Sladky or Dr. Whitton. Tr. 97-98.[27]

c) Dr. Garrett

Dr. Garrett treated Mr. Contreras during his hospitalization in 2003. During this time, Dr. Garrett did not say what caused Mr. Contreras's neurological problem, although Dr. Garrett did recommend the submission of a VAERS report. See exhibit 7 at 106. He did not testify at the hearing.

Dr. Garrett attributed Mr. Contreras's transverse myelitis to his vaccines. Exhibit 13 at 6. Based on his review of the relevant literature, Dr. Garrett asserted that a

> multitude of studies including: case reports, case-series, statistical epidemiological assessments, positive re-challenge or significant exacerbation of symptoms, [and]

[27] The Court appears to have criticized the April 5, 2012 Entitlement Decision for noting that Dr. Wagner's review of material was selective. Opinion and Order, 107 Fed. Cl. at 302.

> review articles all report[ed] a connection between the hepatitis B/DT vaccination and serious neurological reactions.

Exhibit 13 at 12, ¶ 16.

In support of his opinion that the hepatitis B vaccine can cause transverse myelitis, Dr. Garrett referenced five case reports that document the alleged causal relationship. Exhibit 13 at 8-10. He also referenced a CDC report that found "it is biologically plausible for hepatitis B/DT vaccines to cause central nervous system disorders and peripheral nervous system disorders." Exhibit 13 at 12-13. Although paragraph 16 mentioned "statistical epidemiological assessments" as one source that supported a causal connection between the vaccination and a neurological reaction, none of the articles actually submitted to accompany Dr. Garrett's work appears to be an epidemiological assessment. See exhibits 14-21.

Dr. Garrett explained that "[t]he proximity in time to the immunization made the Hepatitis B vaccine and to a lesser extent, the DT vaccine, a suspected cause." Exhibit 13 at 6. Based on his treatment of Mr. Contreras and "extensive review of available medical literature and discussions with colleagues and multiple consultants," Dr. Garrett concluded Mr. Contreras's transverse myelitis was either idiopathic or vaccine-related. Exhibit 13 at 7. Dr. Garrett explained that all the testing and evaluations done on Mr. Contreras to determine a specific cause of his transverse myelitis were "unrevealing," which left him and his colleagues "with etiologies for [Mr. Contreras's] transverse myelitis as either idiopathic or potentially secondary to the recent Hepatitis B vaccination." Exhibit 13 at 7. He could not "find any other reason or condition based on [Mr. Contreras's] medical history and upon [his] examination of [Mr. Contreras] which could have caused [his] condition and illness." Exhibit 13 at 7-8.

d) Dr. Poser

Dr. Poser submitted two reports in support of Mr. Contreras's claim that the hepatitis B vaccine caused him to develop transverse myelitis and GBS. Exhibit 22 at 3, ¶ 4; exhibit 23 at 7, ¶ 15. He did not testify at either hearing. Mr. Contreras asserted that Dr. Poser's opinion provides persuasive evidence for all three Althen prongs. Pet'r's Br. on Remand at 23-30.

Dr. Poser opined that "all vaccines may potentially cause . . . transverse myelitis, or its peripheral equivalent such as GBS in vulnerable individuals." Exhibit 22 at 7, ¶ 10. He explained that the "immune system's response to a viral antigen, be it an infection or vaccine, varies enormously in its manifestations," and includes transverse myelitis and GBS. Exhibit 22 at 8, ¶ 12. Dr. Poser explained that the immune system's "original response" to an antigen, including vaccinations, causes an "inflammation of the vessel wall of cerebral venules and capillaries causing an alteration of the blood brain barrier and permitting water, lymphocytes and other substances, including complement and antibodies, to invade the parenchyma of the nervous system." Exhibit 22 at 8, ¶ 12. This invasion leads to demyelination, which, in turn, leads to neurological complications. Exhibit 22 at 8, ¶ 12. Dr. Poser appears to have suggested that this occurs via molecular mimicry. Exhibit 23 at 3-4 (discussing animal models of experimental allergic encephalitis).

Dr. Poser cited a number of medical literature articles that he claims report on individuals whose neurological complications, including transverse myelitis and GBS, were induced by the hepatitis B vaccine. Exhibit 22 at 4-6; exhibit 23 at appendix. Almost all the articles cited by Dr. Poser are case reports indicating that a neurological disease (such as transverse myelitis or GBS) arose after a vaccination. Many of these articles are listed in a table that appears in section V.C.3.b)(9), below. Almost all of Dr. Poser's second report concerns his view that epidemiological studies cannot establish or disprove the causal relationship between Mr. Contreras's hepatitis B vaccine and his alleged transverse myelitis and GBS because of his "genetic endowment and immunologic history." Exhibit 23 at 6, ¶ 14.

Dr. Poser asserted that "[n]europathologic, radiological and experimental evidence strongly support the causal association between the hep B vaccine and the myelitis-GBS in [Mr. Contreras]." Exhibit 23 at 7, ¶ 14. Dr. Poser did not discuss in any detail the alleged "neuropathologic, radiological and experimental evidence" that, according to him, suggested Mr. Contreras's hepatitis B vaccine caused his neurological complications.

e) Dr. Steinman

Mr. Contreras relied primarily on Dr. Steinman to satisfy Althen prong one. In Mr. Contreras's briefs, he cites to Dr. Steinman frequently. See, e.g., Pet'r's Pre-Trial Br. at 8-12; Pet'r's Post-Hearing Br. at 17-21; Pet'r's Post-Hearing Reply Br., filed Feb. 3, 2011, at 5-9, 14-15, 21; Pet'r's Mot. for Rev. at 24-30; 37-39.

Dr. Steinman opined that the hepatitis B vaccination can cause transverse myelitis via a process known as molecular mimicry and this process can occur within one day. Exhibit 124 at 3. As described in section II.B.3 above, molecular mimicry is a process comprised of several discrete steps.

Dr. Steinman proposed that a molecular mimicry reaction can take place in one day. Dr. Steinman primarily relied upon an analogy to the tuberculin skin test, and a theory based on sensitization. Dr. Steinman cited to many case reports, including the Sinsawaiwong article (exhibit 71 (Suwanna Sinsawaiwong & Pornpen Thampanitchawong, Guillain- Barré Syndome Following Recombinant Hepatitis B Vaccine and Literature Review, 83 J. Med. Assoc'n Thai 1124 (2000))), the Kakar article (exhibit 72 (A. Kakar & P.K. Sethi, Guillain Barre Syndrome Associated with Hepatitis B Vaccination, 64 Indian J. Pediatr. 710 (1997))), and the Tabor article (exhibit 73 (Edward Tabor, Guillain-Barré Syndrome and Other Neurologic Syndromes in Hepatitis A, B, and Non-A, Non-B, 21 J. Med. Virology 207, 209 (1987))).

2. Synopsis of the Secretary's Evidence

a) Dr. Sladky

Respondent's expert, Dr. Sladky, opined that the hepatitis B vaccine does not cause transverse myelitis. Further, Dr. Sladky asserted that an autoimmune process, such as Dr. Steinman's proposed theory of molecular mimicry, could not occur in approximately 24 hours, as Mr. Contreras maintained occurred in his case. Further, Dr. Sladky opined that Dr.

Steinman's proposed theory of molecular mimicry would take at least five days to occur. Thus, Dr. Sladky asserted that Mr. Contreras's hepatitis B vaccine did not cause his transverse myelitis.

Dr. Sladky acknowledged that many illnesses often occur prior to an onset of transverse myelitis, which has led some to suggest a causal relationship. Tr. 300. The most common illness that predates transverse myelitis is an upper respiratory tract infection. Tr. 300. Dr. Sladky opined, however, that whether there is a causal relationship between this (and other illnesses) and transverse myelitis is unknown.

Dr. Sladky opined that a causal relationship between the hepatitis B vaccine and subsequent central nervous system demyelination has not been established. In support of this proposition, Dr. Sladky relied primarily on three epidemiological studies that concluded there was no such causal relationship between the hepatitis B vaccine. See exhibit E (E. Merelli & F. Casoni, Prognostic factors in multiple sclerosis: role of intercurrent infections and vaccinations against influenza and hepatitis B, 21 Neurological Science S852 (2000)); exhibit G (Emmanuel Touze et al., Hepatitis B Vaccination and First Central Nervous System Demyelinating Event: A Case-Control Study, 21 Neuroepidemiology 180 (2002)); and exhibit H (Frauke Zipp et al., No increase in demyelinating diseases after hepatitis B vaccination, 5 Nature Medicine 964 (1999)).[28]

The authors of the Merelli article assessed a number of studies (including the Zipp study (exhibit H) and the Tourbah study (exhibit 34)) that investigated the relationship between the influenza and hepatitis B vaccines and multiple sclerosis. Exhibit E at S853-55. Based on the authors' review of the available literature, they concluded "that there is no scientific evidence suggesting a causal link between [hepatitis B] . . . vaccination and [multiple sclerosis]." Id. at S855. Although none of the experts discussed the Merelli article in their testimony at hearing, Merelli provides some small support that vaccinations do not cause demyelinating diseases in the central nervous system.

The authors of the Touze study assessed the possible association between the hepatitis B vaccine and demyelinating diseases of the central nervous system. Exhibit G at 181. Id. The study was performed on "236 cases and 355 matched controls (117 pairs and 119 triplets)" limited to "patients with a first isolated well-defined neurological event consistent with demyelination involving the optic nerve, spinal cord, the brainstem, the cerebellum or the brain." Id. at 181-82. The patients all had symptoms that lasted more than one day that lacked any explanation. Id. at 181. The authors "postulated that the demyelinating events might be causally linked to [hepatitis B] . . . vaccine if the delay between vaccine injection and onset of the neurological symptoms did not exceed 60 days." Id. at 182. The authors later expanded the range of symptom onset studied to one year after hepatitis B vaccination. Id.

[28] Dr. Steinman also referenced the Touze and Zipp studies in his initial report. See exhibits 75 (Touze) and 76 (Zipp).

The results of the study led the authors to conclude that their study "was sufficiently powerful to rule out a strong association between [hepatitis B] vaccine exposure and a subsequent demyelinating event." Id. The authors cautioned, however, that the study "could not provide a clear indication of a moderately increased risk of a [central nervous system] demyelinating event shortly after [hepatitis B] vaccination in adults." Id. at 181.

The authors of the Zipp study likewise found no causal relationship between the hepatitis B vaccine and demyelinating diseases. Exhibit H at 964. The authors compared the incidence of demyelinating diseases between 27,229 individuals who received the hepatitis B vaccine with 107,469 non-vaccinated individuals. Id. "The rate of central nervous system demyelinating episodes in individuals vaccinated against hepatitis B was compared with that in age- and sex-matched non-vaccinated individuals in the 3 years after vaccination." Id. Based on their findings, the authors concluded that their "results do not support the assumption that hepatitis B vaccination induces demyelination." Id.

Dr. Sladky found these epidemiological studies more informative than case reports. He interpreted the Touze study to conclude that "there is no connection between hepatitis B immunization and multiple sclerosis." Tr. 311. He also found the Zipp study to be "germane," though he acknowledged Caucasians were overrepresented. Tr. 312.

Dr. Sladky discounted the value of case reports due to their bias. Tr. 295-96. According to Dr. Sladky, case reports have at least three different levels of bias. Tr. 295. The first level is the bias of the individual who reports the case. Tr. 295. He considers case report authors to have inherent bias because they look for particular findings and then report them when found. Tr. 295. The second level of bias is due to the publication itself. Tr. 295. As Dr. Sladky explained, "[i]f I report 100 kids who got [a] hepatitis B vaccine and had no side effects, it's not news. It's not going to be reported." Tr. 296. The third level of bias is due to how a case report's findings are subsequently interpreted. Tr. 296. Dr. Sladky considers case reports to be merely phenomenological observations and stated that individuals often incorrectly utilize them to establish causation "when the causality was never established." Tr. 299.

b) Dr. Whitton

Dr. Whitton did not have a firm opinion on which disease (or diseases) afflicted Mr. Contreras because he asserted the hepatitis B vaccine cannot cause transverse myelitis or GBS. See Tr. 438-39. Further, he opined that Dr. Steinman's proposed theory of molecular mimicry could not explain causation of transverse myelitis or GBS occurring in approximately one day, as Mr. Contreras asserts occurred in his case. Tr. 447.

Dr. Whitton rejected the proposition that the hepatitis B vaccine can cause a demyelinating disease. Dr. Whitton based his opinion on multiple studies that investigated whether vaccinations have caused either an increased incidence in a demyelinating disease or a

pre-existing demyelinating disease to worsen.[29] These studies were the foundation for Dr. Whitton's conclusion that "there is no scientifically-acceptable evidence that childhood vaccination causes autoimmune disease." Exhibit L at 5.

Dr. Whitton criticized Dr. Steinman's reliance on case reports. Id. Dr. Whitton opined that "a single case report is of very questionable significance" because the temporal relationship it may document between a vaccination and the onset of an injury is necessary, but not sufficient, to establish causation because "a temporal relationship carries very little weight." Id. at 6.

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[29] The articles Dr. Whitton cited primarily studied two particular demyelinating diseases, multiple sclerosis and GBS. Multiple sclerosis, typically, is a relapsing-remitting disease in which the person suffers demyelination within the central nervous system. See W.C. v. Sec'y of Health & Human Servs., No. 07-456V, 2011 WL 4537877, at *6 (Fed. Cl. Spec. Mstr. Feb. 22, 2011), mot. for rev. denied, 100 Fed. Cl. 440 (2011), aff'd, 704 F.3d 1352 (Fed. Cir. 2013). For articles that found no causal link between hepatitis B vaccination and multiple sclerosis, see exhibit L, tab 5 (Frank DeStefano et al., Vaccinations and risk of central nervous system demyelinating diseases in adults, 60 Arch. Neurol. 504 (2003)) at 504 (analyzing more than 400 subjects and nearly 1,000 controls to determine when the first symptoms of multiple sclerosis or optic neuritis began and finding that "[v]accination against hepatitis B [and four other vaccines] is not associated with an increased risk of multiple sclerosis or optic neuritis"); exhibit L, tab 8 (Alberto Ascherio et al., Hepatitis B vaccination and the risk of multiple sclerosis, 344 N. Eng. J. Med. 327, 327 (2001)) at 337 (a multivariate relative risk exposure analyzing 192 women with multiple sclerosis and 645 matched controls showed "no association between hepatitis B vaccination and the development of multiple sclerosis"); exhibit L, tab 9 (Christian Confavreux et al., Vaccinations and the risk of relapse in multiple sclerosis. Vaccines in Multiple Sclerosis Study Group, 344 N. Eng. J. Med. 319, 319 (2001) at 319 (using European Database for Multiple Sclerosis to determine whether people with multiple sclerosis experienced a relapse within two months of a hepatitis B vaccination and concluding that "[v]accination does not appear to increase the short-term risk of relapse in multiple sclerosis")).

Other studies investigated GBS. See exhibit L, tab 10 (Nakayama & Onoda) at 570 (analyzing registry containing information on more than 67 million vaccinations and looking for incidence of, among other diseases, GBS and acute disseminated encephalomyelitis)); exhibit L, tab 11 (Richard A. Hughes et al., No association between immunization and Guillain-Barré syndrome in the United Kingdom, 1992 to 2000, 166 Arch. Intern. Med. 1301 (2006)) at 1301 (after searching a database with 1.8 million patients, the authors identified cases of GBS within 42 days of various vaccinations (including hepatitis B) and concluded "[t]here is either minimal or no risk of GBS associated with routine immunization practice in the United Kingdom")).

In turn, other articles relied upon some of these studies. These review articles also supported Dr. Whitton's opinion that the hepatitis B vaccine does not cause transverse myelitis. See exhibit L, tab 6 (Ethan Rubinstein, Vaccination and autoimmune diseases: the argument against, 6 Isr. Med. Assoc. J 433 (2004)) at 434 (stating "no risk for autoimmune disease is associated with vaccines against infectious diseases, particularly with childhood vaccines")); exhibit L, tab 7 (David C. Wraith et al., Vaccination and autoimmune disease: what is the evidence?, 362 Lancet 1659 (2003)) at 1665 (an identified mimicry is of little pathogenic importance).

According to Dr. Whitton, establishing causation would at least require "determining whether or not the frequency of [an injury] following any given event (e.g., vaccination) is greater than that which would be expected to occur by chance." Id. Dr. Whitton asserted that several large-scale epidemiological studies have investigated exactly this. In his view, these studies demonstrate that there is no causal relationship between the hepatitis B vaccine and demyelinating diseases. Id. at 5-6, 8.

3. Assessment of Evidence

For purposes of organization, it is helpful to categorize the evidence into two groups. The first group consists of the opinions presented by doctors who treated Mr. Contreras. The second group consists of the opinions presented by doctors whom the parties retained for this litigation. Although this organization is intended to simplify the analysis, the organization is somewhat artificial in that the record is being considered as a "whole." 42 U.S.C. § 300aa-13(a)(1); accord Capizzano, 440 F.3d at 1326.

a) Treating Doctors

Mr. Contreras cited the opinion of two of his treating doctors, Dr. Garrett and Dr. Wagner.[30] See, e.g., Pet'r's Br. on Remand at 3-6. These two doctors, as noted above, did opine that the hepatitis B vaccine caused his neurologic injury. See exhibit 12 at 2, ¶ 6 (Dr. Wagner's affidavit); Tr. 89 (Dr. Wagner); exhibit 13 at 7-8 (Dr. Garrett's affidavit).

In light of these supporting statements, how should they be considered? One potential answer is that the opinions of Dr. Garrett and Dr. Wagner—as treating doctors—should be entitled to so much deference that they are virtually binding as a matter of law. However, this result would be improper for legal and practical reasons.

A suggestion that a special master must always accept the views of a treating doctor is contrary to the statute. Congress stated "[a]ny diagnosis . . . shall not be binding on the special master." 42 U.S.C. § 300aa-13(b)(1). For an example of a pre-Capizzano opinion that found the special master was not arbitrary in weighing the testimony of treating doctors, see Hopkins v. Sec'y of Health & Human Servs., 62 Fed. Cl. 333, 335 (2004). Although the Federal Circuit has instructed special masters to that the views of treating doctors are "quite probative," Capizzano, 440 F.3d at 1326, the Federal Circuit's instruction must be read in accord with the clear words of the statute.

[30] Dr. Kyazze did not opine that Mr. Contreras's transverse myelitis was vaccine-related. Mr. Contreras offers Dr. Kyazze's opinion primarily as evidence that there is no alternative cause for his injuries, which he asserts "provides a firm foundation supporting the opinions of other treating physicians . . . stating that the vaccinations were the cause of the injury to [Mr. Contreras]." Pet'r's Br. on Remand at 14.

Congress's decision to grant special masters relative freedom in evaluating the reports of treating doctors makes sense for practical reasons. In some cases, the treating doctors disagree about aspects of their patient's care, such as diagnosis or etiology. Logically, two divergent views cannot both be binding on special masters. In such cases, special masters weigh the different opinions to determine which is more persuasive. E.g., Broekelshen v. Sec'y of Health & Human Servs., No. 07-137V, 2009 WL 440624 (Fed. Cl. Spec. Mstr. Aug. 18, 2009), mot. for rev. denied, 89 Fed. Cl. 336 (2009), aff'd, 618 F.3d 1339 (Fed. Cir. 2010); Doe 60 v. Sec'y of Health & Human Servs., No. XX-XXXV, 2010 WL 1506010 (Fed. Cl. Spec. Mstr. Mar. 26, 2010), mot. for rev. denied sub nom., Doe v. Sec'y of Health & Human Servs., 94 Fed. Cl. 597 (2010), aff'd, Lombardi v. Sec'y of Health & Human Servs., 656 F.3d 1343 (Fed. Cir. 2011).

Mr. Contreras's case is one in which the treating doctors had different opinions regarding causation. As Mr. Contreras argued, Dr. Wagner and Dr. Garrett stated that the hepatitis B vaccine caused the transverse myelitis. On the other hand, his pediatrician, Dr. Kyazze, was quite forthright in stating that he did not know what caused Mr. Contreras's transverse myelitis. Tr. 60; see supra V.B.1(a). But, Mr. Contreras's infectious disease doctor, Dr. Cheung, stated there was no causal relationship between the hepatitis B vaccine and transverse myelitis. Exhibit 7 at 147. Dr. Cheung came to this conclusion after reviewing literature and considering the amount of time between the vaccination and the onset of neurologic problems. Exhibit 7 at 147. According to a record Dr. Babbitt wrote, Dr. Lake (Mr. Contreras's treating neurologist) and he agreed with Dr. Cheung's opinion that the vaccinations were not causative. Exhibit 7 at 126. Although Mr. Contreras did not cite the statements of Dr. Cheung, Dr. Lake and Dr. Babbitt, these statements are part of the record in this case and must be considered. 42 U.S.C. § 300aa-13(a)(1).

If it is correct that the opinion of a treating doctor is not binding on a special master, then it appears that the special master must necessarily weigh any opinions offered by treating doctors to determine the relative value of divergent opinions. If so, the ensuing question is what factors should the special master use in evaluating those opinions. Although the Federal Circuit stated that the opinions of treating doctors "are favored . . . as treating physicians are likely to be in the best position to determine whether 'a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury,'" Capizzano, 440 F.3d at 1326 (quoting Althen, 418 F.3d at 1280), the Federal Circuit has offered no guidance regarding the weight to give the opinions of treating doctors when their opinions are inconsistent. Similarly, while the Court stated that the April 5, 2012 Entitlement Decision applied the wrong standard "as a matter of law" in evaluating Dr. Garrett, the Court did not identify what factors should be used when comparing the conflicting opinions from treating doctors. See Opinion and Order, 107 Fed. Cl. at 300-01.

Generally, the Federal Circuit has stated that an expert's opinion is only as reliable (or persuasive) as the reasons for the opinion. See Libas, Ltd. v. United States, 193 F.3d 1361, 1366 ("[I]f a trial court relies upon expert testimony, it should determine that the expert testimony is reliable.") (citing Perreira v. Sec'y of Health & Human Servs., 33 F.3d 1375, 1377 n.6, for the proposition that "[a]n expert opinion is no better than the soundness of the reasons supporting it"). Another special master has commented that "[o]bjective factors, including the qualifications, training, and experience of the expert witnesses; the extent to which their

proffered opinions are supported by reliable medical research and other testimony; and the factual basis for their opinions are all significant factors in determining what testimony to credit and what to reject." Tompkins v. Sec'y of Health & Human Servs., No. 10-261V, 2013 WL 3498652, at *4 (Fed. Cl. Spec. Mstr. June 21, 2013), mot. for rev. filed (July 22, 2013); see also Franklin v. Sec'y of Health & Human Servs., No. 99-85, 2013 WL 3755954, at *15 (Fed. Cl. Spec. Mstr. May 16, 2013) (finding written opinion of treating doctor who did not explain the basis for her views less persuasive than the opinions of doctors retained in the litigation).

Here, these factors generally weigh against finding Dr. Garrett's and Dr. Wagner's opinions persuasive on prong one. Although both doctors said that the vaccine did cause Mr. Contreras's injury, and such a statement necessarily implies that the vaccine can cause the injury, see Caves, 100 Fed. Cl. at 145, the doctors did not explain how they reached the conclusion that the vaccine can cause transverse myelitis.

Furthermore, Dr. Garrett's and Dr. Wagner's areas of expertise do not fit very well with the topic of vaccines causing neurologic injuries. Dr. Wagner specializes in emergency medicine, Tr. 64, 91, and Dr. Garrett specializes in pediatrics and pediatric critical care. Exhibit 13 at 1.

In contrast, Mr. Contreras's treating neurologist, Dr. Lake, apparently informed Mr. Contreras's parents that the vaccinations did not cause his transverse myelitis. See exhibit 7 at 126. Her background in neurology makes her more qualified to render an opinion about the cause of a neurologic disease. In addition, Dr. Cheung reached her opinion (that the vaccines were not causative) after reviewing medical articles and studies.

For these reasons, Mr. Contreras does not prevail upon Althen prong one based solely upon the statements of his treating doctors. Consequently, the opinions of the doctors retained for this litigation will be considered next.

b) Dr. Poser and Dr. Steinman

To review, Dr. Poser and Dr. Steinman present the theory that the hepatitis B vaccine can cause transverse myelitis via molecular mimicry. See exhibit 23 at 3, ¶ 5; exhibit 124 at 3.

Molecular mimicry is a theory commonly advanced by petitioners to explain how a vaccine can cause an injury, particularly a demyelinating injury. Molecular mimicry appears in articles published in highly regarded medical journals and Dr. Steinman has written some of these articles. See Tr. 126-128 (discussing exhibits 63, 143-44).[31] Dr. Steinman has testified

[31] Dr. Steinman's experiments have primarily focused on injecting an animal with a substance to see if the animal develops a disease. See, e.g., exhibit 112 (Lawrence Steinman, Blocking Adhesion Molecules as Therapy for Multiple Sclerosis: Natalizumab, 4 Nature Rev. 510 (2005)); see also Tr. 243 (Dr. Steinman stating that he is "a person who has published a lot about mice"). A premise for these studies is that if animals develop diseases, then humans will, too.

about molecular mimicry and he has explained the basic concepts as well as, if not better than, any expert appearing in the Vaccine Program.

c) Daubert Analysis of Molecular Mimicry Theory

Whether the theory of molecular mimicry is a reliable explanation for hepatitis B vaccine causing transverse myelitis is analyzed under Daubert. Terran, 195 F.3d at 1316 n.2 (citing Daubert, 509 U.S. at 592-95). As recognized in Terran, the Daubert factors for analyzing the reliability of testimony are:

> (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and, (4) whether the theory or technique enjoys general acceptance within a relevant scientific community.

Terran, 195 F.3d at 1316 n.2.

(1) Whether the theory of molecular mimicry can be (and has been) tested

The Federal Circuit has alluded to the testability of a theory as a factor that special masters may consider in evaluating a petitioner's expert's theory of causation. See Perreira, 33 F.3d at 1377 ("When the special master asked the expert to support his theory that a vaccine can aggravate a preexisting condition 14 days after the vaccine, the expert acknowledged that it was not supported in the literature and that '. . . it hasn't been studied.' Therefore, we reject the argument that there is support for the expert's opinion."); Moberly, 592 F.3d at 1324 (petitioners' "expert witness testified that the proposed mechanism had never been tested in any peer-reviewed study. Although a Vaccine Act claimant is not required to present proof of causation to the level of scientific certainty, the special master is entitled to require some indicia of reliability to support the assertion of the expert witness.").

The evidence in the record concerning whether the theory of molecular mimicry can be tested to show hepatitis B vaccine can cause transverse myelitis is scant. Dr. Steinman only discussed it briefly at the hearing, see Tr. 544, and Dr. Whitton briefly addressed it in one of his reports. See Resp't's Ex. L at 10. None of the other experts addressed it.

Dr. Steinman explained that his theory is testable and that "it could be done." Tr. 544. Dr. Whitton agreed. Resp't's Ex. L at 10. Dr. Steinman was unaware of any research that specifically sought to determine if the hepatitis B vaccine can cause demyelinating diseases in humans. Tr. 544-45.

Although the parties agreed that Dr. Steinman's theory of molecular mimicry is testable, it has not been tested. This factor does not preponderate in Mr. Contreras's favor.

(2) Whether the theory or technique has been subjected to peer review and publication

According to Dr. Steinman, his proposed mechanism of molecular mimicry is "a theory that is based on a lot of articles by prominent people in the peer reviewed literature." Tr. 123. Dr. Steinman explained that "there's a large number of papers that have been published over the years in support of molecular mimicry." Tr. 124. The "seminal" paper was the 1985 Oldstone & Fujinami paper (exhibit 62), Tr. 124, which Dr. Steinman stated put molecular mimicry "on the map." Tr. 124. Dr. Steinman averred there are now "hundreds if not thousands of . . . exemplifications" of molecular mimicry, and he has written "some of the primary papers" concerning the theory. Tr. 124.

The general theory of molecular mimicry has been explored in numerous peer-reviewed publications in a variety of contexts. But as Dr. Steinman acknowledged, because his more specific theory of hepatitis B vaccine causing transverse myelitis via molecular mimicry has not been tested, it has necessarily not been subject to peer review or publication. As Dr. Steinman testified, none of the articles on which he relied in his reports addressed whether the hepatitis B can cause transverse myelitis. Tr. 191.

In the absence of a peer-reviewed article showing the hepatitis B vaccine causes transverse myelitis, Dr. Steinman relied upon other articles, which, according to Dr. Steinman, support the theory. As a matter of law, Dr. Steinman may rely upon circumstantial evidence to support his opinion. See Capizzano, 440 F.3d at 1325.

Relying on the Bogdanos study,[32] Dr. Steinman opined that the hepatitis B vaccine has been shown to cause an increased production of antibodies that react with myelin. Tr. 152.[33] Dr. Steinman explained that the authors of the Bogdanos article studied the antibody levels in adults before and after receiving the hepatitis B vaccine, and "about 60 percent . . . developed antibodies to hepatitis B that cross reacted with one of the myelin proteins." Tr. 152. Dr. Steinman stated that whether children would have a similar reaction is unknown. Tr. 153.

Dr. Steinman interpreted this study to provide an example of molecular mimicry. Tr. 153. According to Dr. Steinman, an antibody to a myelin protein is significant because it "could be something that leads to an autoimmune demyelinating disease." Tr. 153. However, as Dr. Steinman acknowledged, none of the fifty people in the Bogdanos study actually developed a demyelinating disease. Dr. Steinman distinguished between the production of autoantibodies and the onset of disease. Bogdanos established only that the former happened,

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[32] Exhibit 117 (Dimitrios–Petrou Bogdanos et al., A study of molecular mimicry and immunological cross-reactivity between hepatitis B surface antigen and myelin mimics, 12(3) Clinical & Developmental Immunology 217 (2005)).

[33] Dr. Steinman relied upon Bogdanos even though the subjects were not Hispanic. Tr. 256-57.

not the latter. Tr. 235. Dr. Steinman predicted that if another study were done, then a study involving many more people would identify someone who developed a demyelinating disease after vaccination. Tr. 153-55.

Dr. Whitton was asked about the Bogdanos article. Like Dr. Steinman, Dr. Whitton distinguished between the creation of autoantibodies and the onset of disease. He did not find any evidence that the patients in the Bogdanos study developed autoimmune disease. Furthermore, Dr. Whitton disagreed with the suggestion that a larger study would have found people with an autoimmune disease. Tr. 424.

The undisputed distinction between self-antigens and disease was discussed in an article by David C. Wraith and others. Exhibit L, tab 7. These authors asserted that "an identified mimicry is of little pathogenic importance." They explained "[m]olecular mimicry in itself is not sufficient to trigger autoimmune pathology, and other factors intrinsic to infections, such as tissue damage and long-lasting inflammatory reaction, might be required as well." Id. at 1665.

The Oldstone and Fujinami article, which was written in 1985, provides a foundation for the theory of molecular mimicry. The Bogdanos article moves the theory forward a bit by showing that the hepatitis B vaccine can prompt the production of antibodies that may react with a component of the nervous system. This material makes the theory that the hepatitis B vaccine can cause demyelination possible, and perhaps even plausible.

However, as discussed by Dr. Steinman, Dr. Whitton, and the Wraith article, the onset of disease requires more than just a similar sequence of proteins and the production of auto-antibodies. As Dr. Whitton explained, the lack of disease among the Bogdanos participants is telling. The article demonstrates that the production of autoantibodies does not always cause a disease. In this study, none of the fifty people developed a demyelinating disease after the hepatitis B vaccination. Consequently, the peer-reviewed articles do not support a finding that it is probably correct that hepatitis B vaccine can cause demyelination.

(3) Whether there is a known potential error rate and whether there are methods for controlling the error

This factor is inapplicable to Dr. Steinman's theory of molecular mimicry. Thus, it does not preponderate for or against Mr. Contreras.

(4) Whether the theory or technique enjoys general acceptance within a relevant scientific community[34]

As discussed, the general theory of molecular mimicry is well known and has been the subject of a significant amount of academic research. Doctors generally accept that molecular mimicry explains why some people with rheumatic fever develop Sydenham's chorea. See W.C., 704 F.3d at 1360. But, as Dr. Steinman conceded, his theory that the hepatitis B vaccine can cause transverse myelitis via molecular mimicry has not been studied. Even in the absence of testing, Dr. Sladky opined that a majority of neurologists would accept the proposition that the hepatitis B vaccine can cause transverse myelitis. Tr. 386.[35] He stated, however, that none of them would agree with Mr. Contreras that the hepatitis B vaccine could cause a demyelinating disease within 26 hours. Tr. 386.

Moreover, epidemiological studies "might be needed for a theory to achieve 'general acceptance in the scientific or medical communities.'" W.C., 704 F.3d at 1356. As discussed below, pertinent epidemiological studies have found no evidence that the hepatitis B vaccine can cause demyelinating diseases.

(5) Epidemiological studies

Although petitioners are not required to produce epidemiological studies, they may be considered. Andreu, 569 F.3d at 1379 (citing Daubert, 509 U.S. at 593-97). As discussed, Dr. Sladky and Dr. Whitton relied on epidemiological studies that demonstrated that there is no causal relationship between the hepatitis B vaccine and transverse myelitis. The most on-point and persuasive are the Touze study (exhibit G), the Zipp study (exhibit H), and the Mikaeloff study (exhibit L, tab 29).

The authors of the Touze study assessed the possible association between the hepatitis B vaccine and demyelinating diseases of the central nervous system. Exhibit G at 181. Id. The study was performed on "236 cases and 355 matched controls (117 pairs and 119 triplets)" Id. at 181-82. The authors found that their study "was sufficiently powerful to rule out

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[34] A "general acceptance" in the medical community requires a burden of proof that is significantly higher than that required under the Act because "[i]n medical research, 'attribution of causation is typically not made until a level of very near certainty—perhaps 95% probability—is achieved." Andreu, 569 F.3d at 1379-80 (quoting Liable v. Sec'y of Health & Human Servs., No. 98-120V, 2000 WL 1517672, at *18 (Fed. Cl. Spec. Mstr. Sept. 7, 2000)). Nonetheless, the Federal Circuit before and after Andreu has endorsed a special master's use of the Daubert factors, which include "general acceptance."

[35] Dr. Sladky did not explain the basis for his opinion. Neither party submitted additional evidence that speaks to whether the medical community generally accepts that the hepatitis B vaccine can cause transverse myelitis.

a strong association between [hepatitis B] vaccine exposure and a subsequent demyelinating event." Id. at 182.

The authors of the Zipp study found no causal relationship between the hepatitis B vaccine and, among other things, demyelinating diseases of the central nervous system, such as transverse myelitis. See exhibit H at 964. The authors compared the incidence of central nervous system diseases in 27,229 individuals who had received the hepatitis B vaccine with 107,469 individuals who had not received the hepatitis B vaccine. Id. The authors found that there was "[n]o significant difference between vaccinated and non-vaccinated individuals . . . for demyelinating episodes at any time point analyzed." Id. (citing id. at Table 1). In fact, the authors found "no evidence of demyelination induced by hepatitis B immunization." Id. at 964 (emphasis added).

Another informative study was conducted by a group of French researchers. They identified a group of 356 children who had developed their first episode of demyelination within the central nervous system before they were age 16. The researchers followed these subjects, for an average of 5.8 years, to see whether they developed a second episode of neurological symptoms lasting for more than 24 hours. Exhibit L, tab 29 (Yann Mikaeloff et al., Hepatitis B vaccine and the risk of relapse after a first childhood episode of CNS inflammatory demylination, 130 Brain 1105 (2007)) at 1106-07. The authors concluded that the hepatitis B vaccine "was not associated with a significant increase in the risk of relapse." Id. at 1108.

The type of study Mikaeloff conducted has been recognized as valuable by the Federal Circuit. Mikaeloff evaluated people who already suffered from some type of demyelinating incident within their central nervous system. As such, if the theory that a vaccine could cause demyelination were correct, then this group of participants would be particularly vulnerable to the adverse effects of the vaccination. See exhibit L (Dr. Whitton's report) at 4-8 (describing the value of epidemiologic studies); Tr. 445.[36] The results in Mikaeloff—that people with a previous disorder did not relapse after vaccination—undermine the theory that the hepatitis B vaccination can cause demyelination within the central nervous system. See W.C., 704 F.3d at 1361 (finding that the special master's assessment of epidemiological studies including those looking for relapses of multiple sclerosis after hepatitis B vaccination was not arbitrary or capricious). When Dr. Steinman was asked about the Mikaeloff study, he described it as a "group of competent people," who found data showing that "there's no risk that hepatitis B [vaccine] would push you to have another relapse." Tr. 544.

Epidemiological studies like Touze, Zipp, and Mikaeloff are powerful evidence that the hepatitis B vaccine does not cause demyelinating illnesses. Zipp is a large study involving more than 100,000 people. Mikaeloff investigated people who should, according to the hypothesis that vaccinations lead to demyelination, be especially vulnerable to an adverse consequence. These studies make a finding that the hepatitis B vaccination can cause a demyelinating illness unlikely, although scientific investigations could never establish, with scientific certainty, that

[36] The transcript, unfortunately, does not spell Mikaeloff correctly.

the hepatitis B vaccine absolutely does not cause demyelination. See Tr. 460 ("Science cannot prove all negatives.").

(6) Case Reports

While epidemiological studies are very probative, case reports are not worth much weight. The primary value of case reports is to present a signal that two events (such as vaccination and a disease) have occurred in temporal proximity. This signal may prompt a more vigorous investigation that may or may not support a causal relationship. See Tr. 295-99 (Dr. Sladky), cf. 429-30 (Dr. Whitton stating that he gives "isolated case reports[] very little weight"). According to an article Dr. Garrett cited, "case reports alone are inadequate in answering questions of causation with [autoimmune diseases]." Exhibit 15 (Robert T. Chen et al., Epidemiology of Autoimmune Reactions Induced by Vaccination, 16 Journal of Autoimmunity 309, 310 (2001)).

Some doctors, particularly Dr. Poser, appeared to value case reports more than epidemiological studies. Dr. Steinman also questioned the value of epidemiology in general. He opined that it "doesn't tell you why something happens. It just tells you whether there are numerical differences. Then you can speculate whether it could be due to diet or other factors." Tr. 198-99. For this reason, Dr. Steinman considers case reports to be more persuasive because "the absence of evidence is nowhere near as compelling as the presence of evidence in certain cases." Tr. 195. This view is in conflict with the way scientific studies are usually interpreted. "In the hierarchy of weight of scientific evidence, data from well-designed randomized clinical trials clearly outweighs that from well-controlled observational studies, which in turn, is hierarchically better than uncontrolled observational studies, case series, and then finally, case reports." Exhibit 15 (Chen) at 312. Dr. Sladky and Dr. Whitton shared this approach to weighing evidence.

The predominant view among legal authorities is in accord. The Federal Judicial Center has published a series of guides designed "to assist judges . . . in reaching an informed and reasoned assessment concerning the basis of expert evidence." Jerome P. Kassirer and Gladys Kessler, Preface, in Reference Manual on Scientific Evidence (3d ed. 2011). A pertinent guide states "[a]necdotal evidence usually amounts to reports that events of one kind are followed by events of another kind. Typically, the reports are not even sufficient to show association, because there is no comparison group." David H. Kaye and David A. Freedman, "Reference Guide on Statistics" in Reference Manual on Scientific Evidence at 218. These authors also state "some courts have suggested that attempts to infer causation from anecdotal reports are inadmissible as unsound methodology under Daubert." Id. at 217 n. 14 (citing cases). Reliance upon the Reference Manual from the Federal Judicial Center is appropriate because the burden of proof in an off-Table case, like Mr. Contreras's case, is "the traditional tort standard." Moberly, 592 F.3d at 1322.

The undersigned's view is similar to the position advance in the Reference Manual. Because the parties have included case reports in the record, the undersigned has reviewed those case reports. 42 U.S.C. § 300aa—13(a). The case reports provide little, if any, value in assessing causation.

4. Finding on Althen Prong One

As the party with the burden of proof and as the proponent of the molecular mimicry theory, Mr. Contreras bears the burden of demonstrating that the evidence is persuasive. Althen, 418 F.3d at 1278. It is not enough for Mr. Contreras merely to submit an opinion. The opinion must be reliable. Knudsen v. Sec'y of Health & Human Servs., 35 F.3d 543, 548 (Fed. Cir. 1994); see also Caves, 100 Fed. Cl. at 134-35.

Here, Mr. Contreras has not provided preponderant evidence that demonstrates the reliability of the proposition that the hepatitis B vaccine can cause transverse myelitis (or GBS) via molecular mimicry with respect to the Daubert factors. At best, Mr. Contreras can cite to Dr. Sladky's opinion that most neurologists would accept the proposition that the hepatitis B vaccine can cause transverse myelitis. However, two other Daubert factors—whether it has been tested and whether it has been subject to peer review—do not preponderate in his favor. Further, the epidemiological studies Dr. Sladky and Dr. Whitton referenced found no causal relationship between the hepatitis B vaccine and the incidence of demyelinating diseases. The findings of the epidemiological studies suggest that, contrary to Dr. Sladky's testimony, the theory is not generally accepted. See W.C., 704 F.3d at 1356. Finally, the case reports on which Dr. Steinman, Dr. Poser, and Dr. Garrett rely have minimal value. Accordingly, Mr. Contreras's claim fails on Althen prong one.

C. Prong Three from Althen - Timing

Although the lack of preponderant evidence on Althen prong one means that Mr. Contreras is not entitled to compensation, the Court has directed a review of each Althen prong. Opinion and Order, 107 Fed. Cl. at 296. It is easier to address the third prong, regarding timing, before addressing the second prong.

1. Standards for Adjudicating Althen Prong Three

In Althen, the Federal Circuit stated that a petitioner must provide preponderant evidence of "a showing of a proximate temporal relationship between vaccination and injury." 418 F.3d at 1278. The Federal Circuit elaborated on this aspect of Althen in Bazan, a case in which the petitioner claimed that a booster dose of a Td vaccine caused her to suffer an injury within her central nervous system, known as ADEM, approximately eleven hours after her vaccination. The Federal Circuit stated that this "temporal relationship [was] . . . not such that it is medically acceptable to conclude that the vaccination and the injury [were] . . . causally linked." 539 F.3d at 1352.

The April 5, 2012 Entitlement Decision referenced Althen and Bazan in determining that Mr. Contreras bore the burden of presenting preponderant evidence that his injury occurred within a time-frame that "the medical community would accept . . . for inferring that [his] . . . hepatitis B vaccine caused [his] . . . transverse myelitis." 2012 WL 1441315, at *23. However, the Court held this recitation was erroneous. In its Opinion and Order, the Court stated that the

correct standard is whether the petitioner has shown "that the alleged vaccine injury occurred within a medically-acceptable time-frame." 107 Fed. Cl. at 302.

Pursuant to the Court's instruction, Mr. Contreras must demonstrate by a preponderance of the evidence "that the alleged vaccine injury occurred within a medically-acceptable time-frame" such that it is "medically acceptable to infer causation-in-fact." Opinion and Order, 107 Fed. Cl. at 302 (citing Pafford, 451 F.3d at 1358; Bazan, 539 F.3d at 1352).

2. Onset of Mr. Contreras's Condition: 24-26 Hours after Vaccination

The parties agreed that Mr. Contreras began to experience neurologic problems approximately 24-26 hours after he received his vaccinations. The parties have slightly different arguments about when, in this range, the symptoms actually began. See Resp't's Post-Hearing Br. at 3 n. 5 (acknowledging that the parties disputed when, exactly, Mr. Contreras's symptoms began). The Secretary proposed a relatively earlier onset, see Resp't's Rule 4 Rep't at 9 (approximately 24 hours), and Mr. Contreras proposed a relatively later onset. See Pet'r's Br. on Remand at 42 (26 hours). As discussed in more detail below, whether Mr. Contreras's symptoms occurred in 26 hours or fewer does not affect the outcome of this matter because preponderant evidence establishes that transverse myelitis takes at least a few days to manifest.[37]

3. Medically Acceptable Time-Frame

a) Previous Adjudications

Throughout this litigation, timing was a critical issue. See Opinion and Order, 107 Fed. Cl. at 285. After the initial efforts to resolve the case informally did not succeed (meaning that the case was likely to be tried), the parties obtained supplemental reports. These reports focused on timing. See exhibits 124 (Dr. Steinman), N (Dr. Sladky), and U (Dr. Whitton).

At hearing, much of the testimony concerned whether one day was a medically acceptable time-frame. It was Dr. Steinman's opinion that one day is medically acceptable. See Tr. 166. Among the bases that Dr. Steinman provided for this opinion were case reports and an analogy to tuberculin. In contrast, Dr. Sladky did not accept that one day was an acceptable

[37] Mr. Contreras argued that "the fixation on twenty six (26) hours is misleading on the critical issue of timing for TM" because it is "merely the onset, not the culmination of the evolving diseases." Pet'r's Reply Br. on Remand at 20. Mr. Contreras appears to have argued that, for purposes of Althen prong three, the relevant inquiry is when his condition culminated. See id. This argument is not consistent with Federal Circuit precedent. In several cases, the Federal Circuit has looked to the latency between the vaccination and the onset of the disease. See, e.g., Bazan, 539 F.3d at 1352; Walther v. Sec'y of Health & Human Servs., 485 F.3d 1146, 1147-48 (Fed. Cir. 2007).

interval. He stated that the minimum amount of time was approximately seven days. Tr. 329. Similarly, Dr. Whitton also rejected one day as happening too quickly. In Dr. Whitton's opinion, the minimum amount of time was five days. Tr. 424.

The April 5, 2012 Entitlement Decision resolved Mr. Contreras's case exclusively because he failed to establish that one day was a medically appropriate amount of time to infer that a vaccine can cause transverse myelitis. See 2012 WL 1441315, at *1, 18.

The Entitlement Decision explained and assessed the process of molecular mimicry. 2012 WL 1441315, at *9-10. Specifically, the Entitlement Decision analyzed whether the process of molecular mimicry, as proposed by Dr. Steinman, could occur within approximately 24 hours. Id. at *10-12. As discussed, Dr. Steinman asserted the process could occur within 24 hours whereas Dr. Sladky and Dr. Whitton opined that it would take much longer. See id.

The Entitlement Decision concluded that the opinions of Dr. Sladky and Dr. Whitton were more persuasive on this issue. Aside from one brief case report, none of the medical literature on which the parties' respective experts relied suggested that Dr. Steinman's theory of molecular mimicry could take place in 24 hours. Id. at *18. The medical literature demonstrated "that, at a minimum, the blood brain barrier would prevent an immune-mediated reaction in the spinal cord in one day." Id. at *23.

Specifically, the Entitlement Decision found that six "[r]eports from animal studies support[ed] opinions that a molecular mimicry process takes at least five days to cause damage." 2012 WL 1441315, at *12; see also id. at *13-16. The six articles documented experiments performed on rodents that documented their neurological responses to antigens. In all six experiments, the earliest the rodents manifested neurological problems was many days after exposure to antigens. See exhibit 118 (F. Odoardi et al., Blood-borne Soluble Protein Antigen Intensifies T Cell Activation in Autoimmune CNS Lesions and Exacerbates Clinical Disease, 104(47) PNAS 18625 (2007) (4 days)); exhibit 77 (Juan J. Lafaille, Myelin Basic Protein-specific T Helper 2(Th2) Cells Cause Experimental Autoimmune Encephalomyelitis in Immunodeficient Hosts Rather than Protect Them from the Disease, 186(2) J. Experimental Med. 307 (1997)) (5 days); Exhibit 67 (Scott Zamvil et al., T-cell Clones Specific for Myelin Basic Protein Induce Chronic Relapsing Paralysis and Demyelination, 317 Nature 355 (1985)) at 356 (14 days); Exhibit D (E.P.K. Mensah–Brown et al., Neuroglial Response After Induction of Experimental Allergic Encephalomyelitis in Susceptible and Resistant Rat Strains, 233 Cellular Immunology 140 (2005)) at 142 (11 days); Exhibit K (Divya J. Mekala et al., IL–10–dependent Infectious Tolerance After the Treatment of Experimental Allergic Encephalomyelitis with Redirected CD4CD25 T Lymphocytes, 102(33) PNAS 11817 (2005)) at 11818 (10 days); Exhibit 145 (Rafael L. Ufret–Vincentry, In Vivo Survival of Viral Antigen-specific T Cells that Induce Experimental Autoimmune Encephalomyelitis, 188(9) J. Experimental Med. 1725 (1998)) at 1731 (fig.2) (5 days).

Upon review, the Court vacated the finding of the April 5, 2012 Entitlement Decision. The Court held that the Entitlement Decision imposed on Mr. Contreras an impermissibly high burden of proof with regard to Althen prong three. Opinion and Order, 107 Fed. Cl. at 304. The Court held that the correct standard under Althen prong three is "whether [Mr. Contreras] . . .

established by a preponderance of the evidence that his onset of symptoms occurred within a time-frame for which it is medically acceptable to infer causation-in-fact." 107 Fed. Cl. at 303. Further, the Court held that the Entitlement Decision erred in failing to assign an appropriate amount of weight to the opinions of Mr. Contreras's treating physicians (specifically, Dr. Garrett and Dr. Wagner) with regard to Althen prong three. See id. at 299-302.

b) Synopsis of Evidence

Neither party introduced additional evidence on remand. Thus, the evidentiary record is the same as what was previously considered. Sources of information include: Dr. Wagner, Dr. Garrett, Dr. Cheung, Dr. Poser, Dr. Steinman, Dr. Sladky, and Dr. Whitton. To different degrees, some of these experts relied upon medical literature. The April 5, 2012 Entitlement Decision discussed the literature that the parties had cited in their post-hearing briefs. See, e.g., 2012 WL 1441315 at *13-18. Mr. Contreras, on remand, makes arguments about these articles and literature that were not offered previously. The literature relating to timing includes case reports and animal studies. These sources are reviewed below.

(1) Dr. Wagner

In his affidavit, Dr. Wagner stated "The proximity in time to the immunization made the DT and the Hepatitis B vaccine a suspected cause. I was not able to find any other reason or condition based on the medical history and upon my examination of [Mr. Contreras] which could have caused this reaction." Exhibit 12 at 2, ¶ 6. His testimony was similar. See Tr. 89-90, 93-94.

The Court held, as a matter of law, that the April 5, 2012 Entitlement Decision gave insufficient weight to Dr. Wagner's opinion. 107 Fed. Cl. at 301.

(2) Dr. Garrett

Dr. Garrett claimed that Mr. Contreras developed transverse myelitis "within a medically plausible time period for acute hypersensitivity response." Exhibit 13 at 13. That is, Dr. Garrett considered Mr. Contreras's developing transverse myelitis within 24 hours after his vaccinations to be a medically acceptable time-frame.

Dr. Garrett did not provide any evidence to support this position. In fact, much of the evidence on which he relied in his report suggests otherwise. All of the subjects in the case reports he cited in his report manifested symptoms of neurological complications well beyond 24 hours post-vaccination. None of the subjects developed neurological conditions within 24 hours of vaccination, as Dr. Garrett opined occurred in Mr. Contreras's case. The shortest interval was approximately one week. See exhibit 16 at 2.

(3) Dr. Cheung

Dr. Wagner and Dr. Garrett were not the only treating doctors who offered an opinion regarding the acceptable temporal relationship. Dr. Cheung, who was consulted about Mr. Contreras's case because of her expertise in infectious disease, searched the medical literature to respond to Mr. Contreras's parents' concerns that a vaccination may have caused his transverse myelitis.[38] She stated that "the onset of [Mr. Contreras's] symptoms was quite rapid following the vaccination and other case reports have suggested a slightly longer latency period prior to the actual onset of neurological symptoms." Exhibit 7 at 147. Dr. Cheung, who made this entry as part of her treatment of Mr. Contreras, did not identify the case reports she reviewed.

(4) Dr. Poser

In his initial report, Dr. Poser stated that "the very short latency of the neurological complications following the vaccination, 24 hours, is unusual but does not negate the causal relationship." Exhibit 22 at 3, ¶ 5. Dr. Poser, in his initial report, did not meaningfully address further why the time-frame of Mr. Contreras's case is "unusual," but nonetheless a medically acceptable one. Exhibit 22 at 3, ¶ 5.

Dr. Poser expanded on his opinion in his second report. He conceded that a five-day time-frame is a "usual" one, but maintains it "may not always apply to an individual." Exhibit 23 at 2, ¶ 5. Dr. Poser claimed that Mr. Contreras could have had an autoimmune response to his vaccinations within one day of their administration because "his immune system was in a state of 'high alert'" due to his two previous vaccinations. Exhibit 23 at 3, ¶ 5. Dr. Poser claimed those vaccinations "primed" Mr. Contreras's immune system, which accelerated the response he had to his subject vaccinations. Exhibit 23 at 3, ¶ 5.

(5) Dr. Steinman

Dr. Steinman stated Mr. Contreras's onset of his neurological complications within 24 hours after vaccination was medically acceptable. Exhibit 55 at 3. According to Dr. Steinman, it was more likely than not that Mr. Contreras's vaccines triggered a rapid response, "just as a tuberculin reaction can be elicited within 24-72 hours." Exhibit 55 at 3. In support of this proposition, Dr. Steinman relied primarily on two case reports (the Kakar and Sinsaiwawong articles) and animal models. Id. at 3-4.

The A. Kakar & P.K. Sethi case report (Exhibit 72), Guillain Barre Syndrome Associated with Hepatitis B Vaccination, Exhibit 72, 64 Indian J. Pediatr. 710 (1997), documented an individual that developed GBS within approximately 24 hours after a hepatitis B vaccination. The authors considered the 24-hour onset to be brief compared to other cases of

[38] In some cases, transverse myelitis has appeared after an infection, leading to a theory that infectious diseases trigger transverse myelitis. See exhibit 16 at 3 (stating that infections may trigger transverse myelitis); Tr. 381, 398-99.

vaccine-related GBS. Exhibit 72 at 711. The authors posited two explanations for the rapid onset: "firstly, the patient had been already primed by the antigen and the features were triggered by vaccine; secondly, GBS was unrelated to the vaccine and was caused by a virus in the body." Id. at 711. The authors noted that previous studies had found that the hepatitis B vaccine does not cause GBS. Id.

Other medical literature on which Dr. Steinman relied, however, presents examples in which the latency between an assumed triggering event and the manifestation of GBS was at least a few days. See, e.g., Exhibit 71 (Sinsawaiwong & Thampanitchawong) (case report documenting individual developed first symptoms of GBS three days after hepatitis B vaccine); exhibit 74 (Robert Bakshi & Michael C. Graves, Guillain-Barré syndrome after combined tetanus-diphtheria toxoid vaccination, 147 J. of Neurological Sciences 201 (1997)) (case report documenting individual who developed first symptoms of GBS four days after Td vaccine). Further, other medical literature in the record also indicates that GBS takes at least a few days to manifest. See, e.g., Exhibit 52 at 1 (Erik Boe & Harald Nyland, Guillain-Barré Syndrome after Vaccination with Human Diploid Cell Rabies Vaccine, 12 Scand. J. Infect. Disease 231 (1980)) ("GBS starts frequently 1-3 weeks after various infections and vaccinations.").

Dr. Steinman also relied on animal models to support his opinion that 24 hours was a medically acceptable time-frame. See exhibit 55 at 3-4 (citing exhibit 77 (Lafaille) and exhibit 78 (Rosetta Pedotti et al., An unexpected version of horror autotoxicus: anaphylactic shock to a self-peptide, Nature 216 (2001)); exhibit 105 at 7 (discussing exhibit 118 (Odoardi) and exhibit 78 (Pedotti)).

(6) Dr. Sladky

Dr. Sladky opined that the timing in Mr. Contreras's case was "the most compelling evidence that [his] immunization and demyelinating disease . . . [were] purely coincident." Exhibit I at 3. He opined that "[i]t is virtually impossible to believe that the intricate process of immune activation, tissue targeting and ultimately immunological attack on the nervous system could occur within a 24 hour period." Exhibit I at 3; see also exhibit O at 4 (the 24-hour onset "was implausibly short to invoke causality."). In his opinion, "[e]ven using an optimized immune stimulus in the laboratory, a 24 hour interval between immune challenge and symptoms of demyelinating disease does not occur." Exhibit I at 5 (citing exhibit K (Mekala) and exhibit D (Mensah-Brown)).

(7) Dr. Whitton

In his reports, Dr. Whitton consistently stated that a one-day onset was biologically implausible. Exhibit L at 9; exhibit BB at 2. Dr. Whitton opined that the onset of Mr. Contreras's transverse myelitis one day after his vaccinations was purely coincidental. See exhibit U at 2.

At hearing, his testimony was similar. He stated that estimates about timing are derived from animal models because human beings' response to infections in terms of time "is almost indistinguishable from those that we see in mice." Tr. 437; accord Tr. 476. In experiments with

animals, "the timing is most usually around about ten days. You can play with the systems to shorten it to five [days]." Tr. 424. On cross-examination, Dr. Whitton asserted that "in a clinically healthy individual, . . . I can conceive of no way that hepatitis B vaccine given peripherally could trigger demyelinating disease within 24 hours." Tr. 455-56.

(8) Newly Cited Case Reports

In his briefs on remand, Mr. Contreras cites six pieces of medical literature to support his claim that a 26-hour onset of GBS is medically acceptable. See Pet'r's Br. on Remand at 27-33; Pet'r's Reply Br. on Remand at 6-7.[39] According to Mr. Contreras, these six case reports all recorded "a rapid adverse reaction pertaining to the peripheral nervous system." Pet'r's Reply Br. on Remand at 6.

Jastanian, exhibit 33 (W. Jastanian et al., Complex Regional Pain Syndrome After Hepatitis B Vaccine, 143(6) J. Pediatrics 802 (2003)). The Jastanian case report documented four adolescent girls who developed Complex Regional Pain Syndrome within 60 minutes of receiving the hepatitis B vaccine. Complex Regional Pain Syndrome is "a disorder of one or more extremities that is characterized by pain, swelling, limited range of motion, and vasomotor instability." Exhibit 33 at 802. The authors concluded that the four individuals in the study had "reactions typical of CRPS" within a day of hepatitis B vaccination, but they also concluded that "[a]ttribution of causation is not possible, given the low reported case rate and the absence of long-term follow-up." Exhibit 33 at 804. Furthermore, there is no indication that the etiology of the subjects' conditions was via molecular mimicry.

Tourbah, exhibit 34 (A. Tourbah et al., Encephalitis after Hepatitis B vaccination, 53 Neurology 396 (1999)). The Tourbah article documented eight individuals who developed central nervous system inflammation after receiving a hepatitis B vaccination. Exhibit 34 at 396. None of the individuals, however, showed signs of symptom onset within 24 hours after receiving their vaccinations. The earliest symptom onset was four days after vaccination. Id. at 397. Moreover, none of them developed transverse myelitis (or GBS).

[39] The articles cited in Mr. Contreras's briefs on remand, except for the Kakar article, were not discussed by any of the experts. As the undersigned indicated in a pre-hearing order, "the parties are encouraged to elicit testimony from an expert about the significance of a particular article. Arguments in post-hearing briefs about the relevance of a particular article that has not been the subject of expert testimony may not be persuasive." Order, filed Apr. 1, 2010, at 3; see also Opinion and Order, 107 Fed. Cl. at 288 (discussing, neither negatively nor positively, order to have experts discuss literature). Despite the absence of expert testimony, the articles have been considered. See Moberly v. Sec'y of Health & Human Servs., 85 Fed. Cl. 571, 598 (2009) (special masters "may interpret and apply the conclusions of a medical study introduced into the record by a party, without the guidance of expert witnesses"), aff'd, 592 F.3d 1315 (Fed. Cir. 2010).

Biacabe, exhibit 38 (B. Biacabe et al., A case report of fluctuant sensorineural hearing loss after hepatitis B vaccination, 24 Auris Nasus Larynx 457 (1997)). The Biacabe case report presented an individual who developed hearing loss on the same day he received a hepatitis B vaccine. Exhibit 38 at 457.

Bantz, exhibit 45 (P.M. Bantz et al., Peripheral neurological symptoms after hepatitis B virus vaccination, 96 Q. J. Med. 611 (2003)). The Bantz case report documented a case of an individual who developed vertigo and dysarthria within one day of receiving a hepatitis B vaccination. Exhibit 45 at 611. "On examination, [she exhibited] incomplete paraparesis of the legs and paresis of the arm into which the vaccine was injected." Within five days, her symptoms improved and "no further pathological signs were found upon general, laboratory and neurological examination." Id.

Sinsawaiwong, exhibit 71 (Suwanna Sinsawaiwong & Pornpen Thampanitchawong, Guillain-Barré Syndome Following Recombinant Hepatitis B Vaccine and Literature Review, 83 J. Med. Assoc'n Thai 1124 (2000)). In the Sinsawaiwong case report, the individual studied developed GBS three days after vaccination. Exhibit 71 at 1.

Kakar, exhibit 72, A. Kakar & P.K. Sethi Guillain Barre Syndrome Associated with Hepatitis B Vaccination, 64 Indian J. Pediatr. 710 (1997)). In the Kakar report, the individual developed GBS within 24 hours after vaccination. Exhibit 72 at 1.

(9) Other Case Reports

The previous section described case reports that Mr. Contreras cited in his briefs after remand. Due to the weight that the Court apparently gives to case reports, this section briefly lists additional case reports that describe neurological diseases.[40]

Case Reports of Neurological Diseases Reported After Vaccination		
Exhibit	Title	Symptom and Approximate Onset Interval
34*	A. Tourbah et al., Encephalitis after Hepatitis B vaccination, 53 Neurology 396 (1999)).	Eight cases CNS inflammation (but not transverse myelitis): earliest was four days
18, 35	Lisa M. Tartaglino et al., MR Imaging in a Case of Postvaccination Myelitis, 16 Am. Soc'y of Neuroradiology 581 (1995)	Transverse myelitis: two weeks
16, 37	Luiz Fernando Fonseca et al., Early-Onset Acute	Transverse myelitis: one

[40] For ease of reference, the chart also includes case reports that were described in the previous section. These are marked by an asterisk. The chart does not list the case reports in which the injury was not a neurological injury.

	Transverse Myelitis Following Hepatitis B Vaccination and Respiratory Infection, 61 Arq Neuropsiquiatr 265 (2003)	week
39	Alain Creange et al., Lumbosacral Acute Demyelinating Polyneuropathy following Hepatitis B Vaccination, 30 Autoimmunity 143 (1999)	GBS: one month
40	F. Karaali-Savrun et al., Hepatitis B vaccine related-myelitis?, 8 European J. of Neurology 711 (2001)	four cases of transverse myelitis: six weeks, four weeks, three weeks, three months
19, 41	Hong-Ki Song et al., Acute Myelitis after Hepatitis B Vaccination, 12 JKMS 249, 249 (1997)	Transverse myelitis: two weeks
45*	P.M. Bantz et al., Peripheral neurological symptoms after hepatitis B virus vaccination, 96 Q. J. Med. 611 (2003)).	Vertigo, dysarthria within one day, and later incomplete paraparesis. All problems resolved within five days.
47	C. Iniguez et al., Acute transverse myelitis secondary to hepatitis B vaccination, 31(5) Rev. Neurol. 430 (2000)	Transverse myelitis: one week
48	Jean Poirriez, A preliminary experiment of absorption of antinuclear antibodies by the hepatitis B vaccine components, in a case of neurolupus, 22 Vaccine 3166 (2004)	Transverse myelitis: two months
49, Ex. L, tab 22	M. Khamaisi et al., Guillain-Barre syndrome following hepatitis B vaccination, 22(6) Clin. Exp. Rheumatol. 767 (2004)	GBS: ten weeks
71*	Suwanna Sinsawaiwong & Pornpen Thampanitchawong, Guillain- Barré Syndome Following Recombinant Hepatitis B Vaccine and Literature Review, 83 J. Med. Assoc'n Thai 1124 (2000)).	GBS: three days
72*	A. Kakar & P.K. Sethi, Guillain Barre Syndrome Associated with Hepatitis B Vaccination, 64 Indian J. Pediatr. 710 (1997)).	GBS: within 24 hours
73	Edward Tabor, Guillain-Barré Syndrome and Other Neurologic Syndromes in Hepatitis A, B, and Non-A, Non-B, 21 J. Med. Virology 207, 209 (1987)	Eight cases of GBS: three to nine weeks
74	Rohit Bakshi & Michael C. Graves, Guillain-Barré syndrome after combined tetanus-diphtheria toxoid vaccination, 147 J. Neurological Sciences 201, 201 (1997)	GBS (after Td vaccination): four days
N, tab 2	Douglas A. Kerr & Harold Ayetey, Immunopathogenesis of Acute Transverse Myelitis, 15(3) Current Opinion in Neurology 339 (2002).	Transverse myelitis: two days, nine days

(10) Review Articles

Some of these case reports appear in a different type of article, one that collects many cases. These types of articles are sometimes known as "case series," a term that distinguishes them from case reports.

In this case, the parties submitted the following case series.

Reik, Exhibit 29 (L. Reik, Jr., Neurological complications of immunization, 2 Neurological Infections & Epidemiology 69 (1997)) "Acute transverse myelitis . . . begins three to 14 days after an antecedent immunization in about one-third of cases; the remainder appear to be sporadic." Exhibit 29 at 75. "Postvaccinal cases [of GBS] typically begin seven to 21 days after immunization." Id. at 78.

Tourbah, Exhibit 34. Eight patients developed neurological symptoms 4-49 days after vaccination.

Khamaisi, Exhibit L, tab 22, at 767; exhibit 49 at 767. The authors discussed nine other case reports that documented individuals developing GBS after hepatitis B vaccination. In all but one case report (the Kakar report (exhibit 72)), the onset was more than one day, ranging from three days to nine months. Id. at 768.

Hughes, exhibit L, tab 11 (Richard A.C. Hughes et al., No Association Between Immunization and Guillain-Barré Syndrome in the United Kingdom, 1992 to 2000, 166 Arch Internal Med. 1301 (2006)). The authors reviewed 501 VAERS reports and found that the most common interval of onset of post-vaccinal GBS was two weeks.

(11) Animal Studies

As previously mentioned, there are six animal studies that offer some information about how much time passes between the introduction of a foreign substance and the onset of neurological studies. The observations in those studies range from 96 hours in rodents with damaged blood-brain barriers (exhibit 118 (Odoardi)) to 14 days (exhibit 67 (Zamvil)).

4. Assessment

There appear to be two related aspects to the amount of time that is medically acceptable to infer causation. The first aspect is the amount of time that would typically elapse when a "normal" person receives a vaccine and develops transverse myelitis. The evidence, which is summarized above, varies and the parties have different positions. The resolution is set forth in section a, below.

Regardless of the outcome on this general idea, Mr. Contreras identifies various factors that suggest, at least to Mr. Contreras, that his particular response to the vaccinations would be

faster than everyone else's response. These potentially modifying factors are discussed in section b, below.

a) Timing in General

The Entitlement Decision discussed a number of articles that pertained to the timing aspect of Dr. Steinman's theory of molecular mimicry. See 2012 WL 1441315, at *12-16. That analysis is incorporated here. That analysis concluded that molecular mimicry could not cause transverse myelitis within one day. 2012 WL 1441315, at *23-24.

In its Opinion and Order, the Court held that on remand the undersigned "may not disregard case reports" that pertain to the issue of timing. Contreras, 107 Fed. Cl. at 309. In accord with the Court's instruction, the case reports have been reviewed again.

With perhaps four exceptions, the case reports present examples in which GBS and transverse myelitis developed much more than 24 hours. It is difficult to see how, for example, a report that transverse myelitis developed one week after vaccination (exhibit 47 (Iniguez)) or a report that transverse myelitis developed two months after vaccination (exhibit 48 (Poirriez)) supports a proposition that one day is a "time-frame for which it is medically acceptable to infer causation-in-fact." Opinion and Order, 107 Fed. Cl. at 303.

The times involved in the overwhelming majority of case reports are much longer than the time involved in Mr. Contreras's case. These cases and the reports from Reik and Hughes (reporting that post-vaccinal cases of GBS begin 7-21 days after vaccination and the most common interval between vaccination and GBS was two weeks, respectively) are entirely consistent with the opinions of Dr. Sladky and Dr. Whitton. Dr. Sladky stated a one-day onset was "virtually impossible." Exhibit A at 3. Dr. Whitton stated that it was "exceedingly unlikely" that Mr. Contreras could have developed an immune response to his vaccinations within 24 hours. Exhibit N at 9.

This material is also consistent with Dr. Poser's description of the "usual" interval between vaccination and the onset of neurological problems—five days. Exhibit 23 at 3, ¶ 5.

Within the universe of case reports, the most prominent exceptions are the case reports from Kakar, Sinsawaiwong, Biacabe, and Bantz. Previously, Kakar was found unpersuasive because its limited value of an isolated incident was outweighed by the value of controlled scientific experiments such as Odoardi. Entitlement Decision, 2012 WL 1441315, at *13. The Court did not comment upon this analysis. Thus, it appears that the Court accepted the way that Kakar was weighed was within the undersigned's discretion. See Opinion and Order, 107 Fed. Cl. at 309, n.42.

The Sinsawaiwong case report documented a 17-year-old who developed GBS three days after she received a hepatitis B vaccine. Exhibit 71 at 1. The authors found that "[t]he temporal relationship between GBS and vaccination was suggestive of a vaccine-induced cause." Id. The authors stated that "[a]lthough [they] . . . could not definitely prove a causal link between GBS and the vaccination, GBS occurring after the first dose suggested that further

doses be withheld." Id. at 2. The authors noted that the three-day onset was shorter than other previous reports with which they were familiar. Id. (noting that "clinical features [of neurological complications] develop[ed] 2-6 weeks after [hepatitis B] vaccinations of varying doses").

The Biacabe case report presented an individual who developed hearing loss on the same day on which he received a hepatitis B vaccine. Exhibit 38 at 457. Dr. Poser cited this case report in support of the proposition that it is one of "[m]any well documented cases of central and peripheral [nervous system] complications" considered to have been induced by the hepatitis B vaccine. Exhibit 23 at 5, ¶ 10. None of the experts discussed this case report at the hearings. Thus, it is difficult to assess the relevance to transverse myelitis, a demyelinating disease of the spinal cord.

Similarly, the significance of the Bantz case report is not readily apparent because none of the experts testified about it. The woman discussed in that article was not diagnosed as having transverse myelitis or GBS. Further, it appears that that her disease was much less severe than the disease that afflicted Mr. Contreras because she displayed no signs or symptoms of a disease five days after vaccination. See exhibit 45.

The Court was troubled by the way Dr. Garrett's and Dr. Wagner's opinions were weighed. Opinion and Order, 107 Fed. Cl. at 299. In the original April 5, 2012 decision, Dr. Garrett's and Dr. Wagner's opinions were found unpersuasive for various reasons. 2012 WL 1441315, at *22-23. The Court held, as a matter of law, that value placed upon Dr. Garrett's and Dr. Wagner's opinions was inappropriate. Consequently, Dr. Garrett's and Dr. Wagner's opinions must be reconsidered.

Again, a tension exists in evaluating the opinions of the treating doctors in the presence of an inconsistent opinion from another treating doctor. Although Dr. Garrett and Dr. Wagner each stated that the onset occurred within a medically acceptable time-frame, exhibit 13 at 12, ¶ 16; exhibit 12 at 3, ¶¶ 3, 6, Dr. Cheung did not agree. Her opinion was that Mr. Contreras's onset was more rapid than the latency reported in the medical literature she reviewed. Exhibit 7 at 147. When treating doctors come to different conclusions about whether their patient's disease arose in a "time-frame for which it is medically acceptable to infer causation-in-fact," how can a special master credit (or favor) both opinions?

Additionally, the opinions of Dr. Garrett, Dr. Wagner and Dr. Cheung must be considered as part of the record as a whole, 42 U.S.C. § 300aa-13(a)(1), which includes the opinions of Dr. Poser, Dr. Steinman, Dr. Sladky, and Dr. Whitton. The Federal Circuit has not directly stated that a special master must automatically adopt or defer to any one source of information. See Whitecotton v, Sec'y of Health & Human Servs., 81 F.3d 1099, 1108 (Fed. Cir. 1996) ("Congress desired the special masters to have very wide discretion with respect to the evidence they would consider and the weight to be assigned that evidence"); accord 42 U.S.C. § 300aa-13(b)(1) ("Any diagnosis . . . shall not be binding on the special master.").

In terms of the value of treating doctors with respect to timing, Bazan is illuminating as to the proper approach for special masters. In Bazan, the petitioner received a booster dose of

the tetanus-diphtheria vaccine and developed a disease of her central nervous system, acute disseminated encephalomyelitis (ADEM), approximately 11 hours later. See Bazan v. Sec'y of Health & Human Servs., 70 Fed. Cl. 687, 699 (2006) (finding preponderant evidence that "petitioner had previously received several tetanus vaccinations"), rev'd on other grounds, 539 F.3d 1347 (Fed. Cir. 2008). To support her claim that the vaccination caused the ADEM, Ms. Bazan presented the testimony of her treating doctor, Dr. Hansen. Bazan, 539 F.3d at 1352. In opposition to this claim, the Secretary presented the testimony of a doctor retained for the litigation, Dr. Sriram. Id. The special master discussed the testimony and the articles on which the experts relied. Id. at 1353. The special master credited Dr. Sriram's opinion over the opinion of the treating doctor and found that the petitioner "had not proven by a preponderance that eleven hours is a medically acceptable timeframe within which ADEM could manifest after her vaccination, and that [the petitioner] had failed to prove the 'proximate temporal relationship' element of her prima facie case as a result." Id.

When the case reached the Federal Circuit, the Federal Circuit reviewed the special master's determinations. The Federal Circuit held that "the special master's reliance on the government's evidence was lawful" and the special master appropriately found that "Dr. Sriram's testimony was more credible and probative than that of [petitioner's treating physician] Dr. Hansen." Id. at 1354. Thus, Bazan supports an approach in which all evidence is weighed. If a special master were required to accept the opinion of the treating doctor always, an approach arguably suggested in Capizzano, then the Federal Circuit would have vacated the special master's decision in Bazan because the special master did not credit Dr. Hansen's opinion. Consequently, and consistent with Bazan, the entire record needs to be reviewed.

In light of the record as a whole, the undersigned finds the testimony of Dr. Whitton to be the most persuasive. Among all the specially retained witnesses who testified at the hearing, Dr. Whitton's demeanor suggested that he approached the question from a non-partisan perspective. Although special masters may make "credibility determinations" when assessing an expert's opinion, Moberly, 592 F.3d at 1325-26, the persuasiveness of Dr. Whitton's opinion rests on much more than just his demeanor.

An important reason for crediting Dr. Whitton's opinion that the minimal amount of time for molecular mimicry exceeds one day is a study that he helped to conduct. In this experiment, researchers attempted to determine how quickly mice activated a particular aspect of their immune system known as memory T cells. (Memory T cells are a foundation for the protective aspect of immunization.) Dr. Whitton's group of researchers found that "[m]emory cells like naïve cells, begin to divide only after lengthy (2–3 day) delay after virus infection, and their subsequent rate of division is no faster than that of naïve cells." Exhibit L, tab 31 (Jason K. Whitmire, Tentative T Cells: Memory Cells Are Quick to Respond, but Slow to Divide, 4 PLos Pathogens e1000041 (2008)) at e1000042.

When questioned about this work, Dr. Steinman acknowledged that Dr. Whitton's work is a "beautiful study . . . published in a great journal." However, Dr. Steinman attempted to distinguish this article as not informing what happens with human beings because Dr. Whitton's group experimented on rodents. Tr. 251-52 (Dr. Steinman). The attempt to distinguish rodents from humans, especially in regard to Dr. Steinman's proposed analogy to tuberculin, was found

unpersuasive. 2012 WL 1441315, at *18-19. The Court accepted that the analysis of tuberculin was within "the special master's function" of "weighing evidence for persuasiveness." 107 Fed. Cl. at 306.[41] Consequently, the Whitmire article supports Dr. Whitton's opinion.

To rebut Dr. Whitton's opinion that molecular mimicry takes multiple days, Dr. Steinman cited to the Odoardi article. Exhibit 105 (Supp'l Rep't) at 7, citing exhibit 118 (F. Odoardi et al., Blood-borne Soluble Protein Antigen Intensifies T Cell Activation in Autoimmune CNS Lesions and Exacerbates Clinical Disease, 104(47) PNAS 18625 (2007)). In his view, Odoardi showed mice developing a lesion in the central nervous system 24 hours after the injection of a substance that was equivalent to a vaccination. Tr. 174-75.

Dr. Whitton disagreed. Dr. Whitton explained that the effector T cells became active only after the blood-brain barrier was breached, which, in the Odoardi experiment, was 96 hours after the injection. Thus, Dr. Whitton indicated that this portion of Odoardi did not provide information about how long T cells would take to damage Mr. Contreras's brain because his blood-brain barrier was intact. Tr. 480-82.

Because Odoardi offered potentially strong support for finding that molecular mimicry can happen in one day (and therefore would support a finding that one day is a medically acceptable time-frame for which to infer causation), the undersigned requested additional testimony from Dr. Steinman and Dr. Whitton about this article. At the supplemental hearing, Dr. Whitton stated that Dr. Steinman did not understand the experiment correctly. Tr. 633. Dr. Steinman did not present any persuasive response.

The Entitlement Decision reviewed, in detail, the Odoardi findings and the expert's explanation of them. 2012 WL 1441315, at *13-14. Without repeating this analysis, the bottom line is that an article that Dr. Steinman cited to support his opinion that one day is a medically acceptable time-frame for an injection of an antigen to stimulate the production of T cells that breach the blood-brain barrier and damage the central nervous system did not actually show that. Instead, the article "actually strengthen[] [Dr. Whitton's] convictions that this just can't have happened in a healthy boy within 24 hours." Tr. 642.

Although it is certainly true that petitioners are not required to submit medical literature to establish their claims, Althen, 418 F.3d at 1280, it is also true that special masters do not have to accept the opinion of an expert simply because an expert said it. Cedillo v. Sec'y of Health & Human Servs., 617 F.3d 1328, 1339 n.3 (Fed. Cir. 2010). It also true that when literature is submitted, special masters may review that literature. Andreu, 569 F.3d at 1379.

[41] The Court indicated that the analogy to tuberculin should be reconsidered because the blood-brain barrier may be irrelevant to Mr. Contreras's presentation. 107 Fed. Cl. at 306 n.40. However, as explained above in sections V.C and V.A.1, the June 18, 2003 MRI shows a breach in Mr. Contreras's blood-brain barrier. Thus, the analogy to tuberculin remains unpersuasive.

Here, the literature that Dr. Whitton cited supports his opinion. In contrast, the Odoardi article, which appeared to be an important article supporting Dr. Steinman's opinion, actually did not support it. Dr. Steinman's reliance on Odoardi makes his testimony less credible and less persuasive. Consequently, the persuasive evidence supports a finding that a medically acceptable time-frame to infer causation exceeds one day and is probably approximately five days.

b) Potentially Modifying Factors

Since Mr. Contreras has not established that an immune-mediated reaction can cause transverse myelitis within one day under normal circumstances, the next question is whether any unusual features about Mr. Contreras's case would change the typical response time. Mr. Contreras has proposed five factors: (1) his previous receipt of the hepatitis B vaccine (also known as "priming"), (2) his Hispanic ethnicity, (3) his receipt of two vaccines at the same time, (4) the presence of an adjuvant, alum, and (5) his prior exposure to the Epstein-Barr virus and mycoplasma pneumoniae. These are discussed in turn.

(1) Priming

The Entitlement Decision noted that there was "relatively little evidence about whether previous doses of a vaccination make a recipient more likely to develop an adverse response within one day." 2012 WL 1441315, at *20. Most of the evidence on this issue came from the testimony of Dr. Steinman and Dr. Whitton at the hearings because neither party cited relevant medical literature. Id. Dr. Steinman opined that Mr. Contreras's previous hepatitis B vaccinations "primed" him to have a faster response to his June 16, 2003 hepatitis B vaccine. Id. at 21.

The Entitlement Decision found Dr. Steinman's opinion on this issue unpersuasive. Id. As both Dr. Steinman and Dr. Whitton noted, in multiple animal experiments, when "primed animals developed an adverse reaction, the interval was several days." Id.

In its Opinion and Order, the Court questioned whether the undersigned "was permitted to use a preponderance standard to 'accept' [Mr. Contreras's] evidence" regarding the priming issue in the Entitlement Decision. 107 Fed. Cl. at 304. The Court could not discern if the Entitlement Decision held that Dr. Steinman's priming argument could not be considered or whether it found the priming argument to be unpersuasive. Id. at 305 The Court found, however, "[i]t is more likely . . . that the [undersigned] . . . meant that he did not find the 'priming' theory advanced by Dr. Steinman and Dr. Poser to be persuasive." The Court concluded that "[t]o the extent that the [undersigned] . . . mistakenly characterized his inquiry into 'priming' as a determination of the preponderance of the evidence on this issue, but actually ruled on the persuasiveness of petitioner's argument, this was harmless error." Id. Thus, the Court ordered the undersigned to "explain whether or not Dr. Poser's opinion, and Dr. Steinman's opinion, are together more persuasive than the opinions of respondent's experts on the priming issue." Id. at 305 n. 37. As discussed below, Mr. Contreras's argument on the issue of priming is unpersuasive.

In light of the Court's instruction, the evidence regarding priming is again reviewed. Dr. Poser opined that Mr. Contreras's "nervous system reaction was 'primed' by his two previous vaccinations." Exhibit 23 at 3, ¶5. This caused his immune system to be "in a state of 'high alert' against the hepatitis B antigen," which led to an "abnormal response" from his immune system that was "accelerated by" his third and final hepatitis B vaccination. Id.

Dr. Steinman did not discuss the "priming" issue in his reports, but he discussed it during his testimony at the hearing. According to Dr. Steinman, "priming" essentially means that Mr. Contreras's immune system was more sensitive to his June 13, 2013 hepatitis B vaccination because of the two previous ones he had received. See Tr. 161, 673. This "priming" of Mr. Contreras's immune system led to an unusually rapid response to his June 16, 2003 hepatitis B vaccine. See Tr. 161, 612-13, 675.

Dr. Steinman opined that Mr. Contreras's earlier exposures to the hepatitis B vaccine made him comparable to the diseased rodents from the Odoardi experiment that had T cells in their brains within one hour of being injected with myelin basic protein.[42] E.g., Tr. 599; Tr. 604; Tr. 618; Tr. 673–74; see also Tr. 161. Dr. Steinman also stated that when there is sensitization, the adverse reaction occurs very quickly. Tr. 612-13.

However, Dr. Whitton opposed Dr. Steinman's opinion. Dr. Whitton stated that he did not see why Mr. Contreras's previous exposure to the hepatitis B vaccine would make him more likely to develop a disease in his central nervous system. Tr. 461, 646.

In effect, the record contains the opinion of two extremely qualified doctors presenting opposite opinions regarding the effect, if any, of prior doses. Neither party has cited any studies about priming. Thus, the undersigned must weigh the relative value of the experts' testimony and accept Mr. Contreras's evidence when it weighs even slightly in his favor. Moberly, 592 F.3d at 1325-26; Althen, 418 F.3d at 1280-81.

Dr. Steinman's reasoning is unpersuasive. Dr. Steinman is saying that although rodents may need days to develop an immune-mediated adverse reaction in their central nervous system, Mr. Contreras can develop the same type of reaction in only one day because he was different from the rodents. Mr. Contreras, according to this portion of Dr. Steinman's presentation, was "primed."

The flaw in Dr. Steinman's reasoning is the implicit assumption that the rodents were "normal." Actually, the rodents in these experiments are genetically designed to develop the adverse reaction. There is no dispute that these rodents are "primed."

[42] Dr. Steinman's analogy to the Odoardi rodents in this context seems inconsistent with his testimony that the rodents in other experiments, such as Lafaille, which showed an onset of experimental autoimmune encephalitis in approximately four to five days, did not provide useful information about human beings. Tr. 575; see also tr. 217-18.

Dr. Steinman explained how the animals are prepared. With reference to Lafaille, in which the animals showed neurologic disease four to five days after the introduction of an antigen, Dr. Steinman stated

> They [the Lafaille researchers] took mice and they made animals that every single T cell in their whole body was able to recognize one of those peptides from myelin basic protein. And then they polarized them either to make a lot of gamma interferon or to make a Th2 cytokine probably [IL-4]. Then they put them into immune deficient animals so that the recipient animal would have no T cells of its own, and they asked could both the Th1 and/or the Th2 type of T cell cause EAE.

Tr. 217. When asked whether these animals were "preprimed," Dr. Steinman responded "Definitely." Tr. 217. Later, Dr. Steinman characterized the animal studies as "very contrived experiments." Tr. 525.

Dr. Whitton agreed that the animals were manipulated. He stated that "[t]he deck has been stacked in order to investigate a scientific possibility." In his opinion, the laboratory conditions are "optimized" to show a response. Tr. 424–25.

When these primed rodents developed an adverse reaction, the interval was several days. Thus, even if Mr. Contreras were assumed to be primed for a reaction, the likely amount of time would still be measured in days. Neither Dr. Steinman nor Dr. Poser presented persuasive reasons for finding that Mr. Contreras would react faster than rodents that are programmed to have an adverse reaction.

(2) Mr. Contreras's Hispanic Ethnicity

Mr. Contreras asserted that his Hispanic ethnicity explains, in part, why he had an adverse response to his hepatitis B vaccination. Dr. Steinman opined that Hispanics have immunological responses to antigens, such as the hepatitis B vaccine, that are different from the responses that individuals from other ethnic backgrounds have. See Notice of Filing/Table of Contents Vol. XXVII, filed April 15, 2010, at 1 ("Exhibits 132-134 and 136-142 are filed to support Dr. Steinman's opinion about Hispanics having a different immunogenetic background.").

Dr. Steinman opined that Hispanics, like Mr. Contreras, have a stronger immunological response to the hepatitis B vaccine than other ethnic groups. For this reason, he questioned the reliability of the epidemiological studies on which Dr. Sladky relied. Dr. Steinman did not contest the findings or conclusions of the epidemiological studies cited by Dr. Sladky that showed the incidence of demyelinating diseases did not increase after hepatitis B vaccination. Dr. Steinman's primary criticism is that he believed that Hispanics, like Mr. Contreras, were not adequately represented in any of studies. Tr. 191-92. He opined the lack of representation of

Hispanics in the studies renders them irrelevant to Mr. Contreras's case. See Tr. 192-93; Tr. 258.[43]

During the hearing, Dr. Steinman discussed many, but not all, of the pieces of literature that concern Hispanics. Dr. Steinman stated that the Cunningham[44] article demonstrated that "Hispanics are responding differently" to the hepatitis B vaccine. Tr. 170. He cautioned, however, that he "wouldn't take it for more than it is." Tr. 170.

The Chitnis[45] article compared the incidence of multiple sclerosis among various ethnic groups. Within those groups, the authors also compared the incidence of multiple sclerosis in minors and adults. Exhibit 134 at 1. Dr. Steinman opined that the results of this study demonstrate that an individual's ethnic background "really does matter" when determining how an individual will "respond to a hepatitis B vaccine as an adolescent or how [one] might be susceptible to developing multiple sclerosis." Tr. 172.

The Secretary disputed Mr. Contreras's argument that he rapidly responded to the hepatitis B vaccine due, in part, to his Hispanic ethnicity. Dr. Sladky disagreed with Dr. Steinman's opinion that Hispanics have a response to the hepatitis B vaccine that is different and/or stronger than those from other ethnic backgrounds. He was unaware of any evidence that suggested Hispanics are more vulnerable to the hepatitis B vaccine. Tr. 301.

Dr. Whitton did not dispute that the genetic makeup of some individuals can make them more susceptible to developing certain diseases. He acknowledged there are studies that have been conducted to measure "the effects of vaccination in individuals who are known to be susceptible to a particular disease," id. at 8, but he was not aware of any evidence that suggested an individual's Hispanic ethnicity would make him or her more susceptible to developing transverse myelitis. Tr. 433.

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[43] As the Secretary noted, "Dr. Steinman acknowledged that the one case study upon which he heavily relies [the Kakar case study, exhibit 72] involves a . . . child from India, an individual who is not Hispanic. . . . Dr. Steinman also agreed that he could not find any case reports concerning an alleged adverse reaction to the Hep[atitis] B vaccination in individuals of Hispanic heritage." Resp't's Post-Hearing Br. at 13 (citing Tr. 194-96). Mr. Contreras did not respond to the Secretary's critique of Dr. Steinman's inability to provide a case report concerning an individual of Hispanic ethnicity who had an adverse reaction to the hepatitis B vaccine in spite of his reliance on case reports. See Pet'r's Reply to Respondent's Post-Hearing Br. at 21.

[44] Exhibit 132 (C. Cunningham et al., Randomized Trial to Determine Safety and Immunogenicity of Two Strategies for Hepatitis B Vaccination in Healthy Urban Adolescents in the United States, 29:6 Pediatric Infectious Disease J. 1 (2010)).

[45] Exhibit 134 (T. Chitnis et al., Demographics of pediatric-onset multiple sclerosis in an MS center population from the Northeastern United States, 15 Multiple Sclerosis 627 (2009)).

Aside from Dr. Steinman's testimony, the only evidence in the record that speaks directly to the issue of whether Hispanics are generally more susceptible to developing neurological complications due to the hepatitis B vaccine are the Cunningham (exhibit 132) and Chitnis (exhibit 134) articles. The other eleven pieces of literature Mr. Contreras submitted to support his argument on this issue do not pertain to the hepatitis B vaccine and/or transverse myelitis.

Dr. Steinman and Mr. Contreras did not connect many of these studies to Mr. Contreras's case. For example, although two studies purported to find Hispanics (or Mexican-Americans) suffered an increased incidence of diabetes, see exhibits 135[46], 137[47], this fact tells little, if anything, about transverse myelitis. And the question about whether a vaccine can cause transverse myelitis is even further removed. Other studies about Hispanics seem similarly removed from Mr. Contreras's case. There were articles about intussusception (exhibit 133[48]), lupus (exhibit 139[49]), and autoimmune hepatitis (exhibit 138[50]).

The articles that appear to have any significance are Chitnis and Cunningham. According to Dr. Steinman, the Cunningham study simply documented that "Hispanics are responding differently" to the hepatitis B vaccine. Tr. 170. Dr. Sladky did not dispute this finding. See Tr. 362. But, Dr. Steinman indicated that it has limited value in explaining how Mr. Contreras's Hispanic ethnicity could have contributed to his alleged reaction to his hepatitis B vaccine. See Tr. 170-71. Likewise, the authors of the Chitnis article found that the varied incidence of

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[46] Exhibit 136 (L.I. Garner et al., Prevalence of Diabetes in Mexican Americans. Relationship to percent of gene pool derived from Native American sources, Diabetes Journal;

[47] Exhibit 137, M.I. Harris, Epidemiological correlates of NIDDM in Hispanics, Whites, and Blacks in the U.S. Population, Diabetes Journal).

[48] Exhibit 133 (Jacqueline E. Tate et al., Trends in Intussusception Hospitalizations Among US Infants, 1993-2004: Implications for Monitoring the Safety of the New Rotavirus Vaccination Program, 121:5 Pediatrics 1125 (2008)).

[49] Exhibit 139 (J. Reveille et al., Systemic Lupus Erythematosus in Three Ethnic Groups. I. The effects of HLA class II, C4, and CR1 Alleles, Socioeconomic Factors, and Ethnicity on Disease Onset, 41:7 Arthritis and Rheumatism 1161 (1998)). Mr. Contreras also cited a news article where an interviewee, the president of the Lupus Research Institute, stated that Hispanics "experience a higher rate of lupus." Exhibit 141 at 1, "Lupus Research Institute Launches Spanish-Language Campaign to Alert Hispanic Women to the Dangers of Lupus," Lupus Research Institute (Sept. 6, 2005); see also exhibit 142 at 2, "Human Genome Sciences, Inc.: Novel Evidence-Based Systemic Lupus Erythematosus SLE Responder Index Described in Peer Reviewed Publication as Potentially Significant Advance in Lupus Drug Development," Drug Week (Sept. 25, 2009) (stating that Hispanic women are at increased risk for lupus).

[50] Exhibit 138 (J. Ahn et al., African Americans, Hispanics/Latinos and Women Present More Frequently with Acute Autoimmune Hepatitis: Preliminary Report from the North American Autoimmune Hepatitis Study Group).

multiple sclerosis among different ethnic groups, including Hispanics, was noteworthy. Dr. Sladky interpreted the article's finding to demonstrate that Hispanics "are more apt to develop symptoms [of multiple sclerosis] earlier [than other ethnic groups]." Tr. 363. He opined, however, that the findings are problematic because of small sample size of Hispanics. Tr. 364. Further, Dr. Sladky was "not familiar with any data suggesting that Hispanic ancestry is a risk factor for autoimmune neurological diseases." Exhibit P at 2.

(3) Td and Hepatitis B Vaccine Combination

In Dr. Poser's report, he stated that Mr. Contreras's transverse myelitis was "unquestionably the direct result of the administration of the hepatitis B/DT vaccine." Exhibit 22 at 3, ¶ 5. Dr. Poser also opined that the "unusually rapid" onset of Mr. Contreras's transverse myelitis "may have been [due to] the combination [of the hepatitis B vaccine] with [the] TD [vaccine]." Exhibit 23 at 2-3. However, his reports and supporting literature concern primarily the hepatitis B vaccine.

Some support for Dr. Poser's assertion that the combination of vaccines contributed to Mr. Contreras's purported adverse reaction was a quotation from "page 96 of the Immunization Safety Review, para[graph] 2 of Conclusions." Exhibit 23 at 3, ¶ 5. According to Dr. Poser, this source states, "multiple immunizations . . . could possibly influence an individual's risk of autoimmunity." Id. The source of this quotation is unclear because Dr. Poser did not provide a citation for the "Immunization Safety Review" document, nor has the source been filed into the record. Thus, it is difficult to give Dr. Poser's opinion much weight. Snyder ex rel. Snyder v. Sec'y of Health & Human Servs., 88 Fed. Cl. 706, 745 (2009) (quoting Gen. Elec. Co. v. Joiner, 522 U.S. 136, 146 (1997)) (a special master is not required to rely on the ipse dixit of an expert).

In his reports, Dr. Steinman stated that Mr. Contreras's Td vaccine "served as a further adjuvant to trigger [GBS]. DT immunization has been reported in association with [GBS] . . . in children." Exhibit 55 at 3 (citing exhibit 74) (Bakshi & Graves). Dr. Steinman did not take a firm position on whether Mr. Contreras's Td vaccine contributed to his condition. He testified that it "could have added to [Mr. Contreras's condition], but without the hepatitis B vaccine, we would not be in court today." Tr. 118. He did, however, testify later that the Td vaccine hastened his immune response. Tr. 621.

Dr. Whitton disagreed. He did not believe there was any evidence that could implicate Mr. Contreras's Td vaccination or any evidence that the Td and hepatitis B vaccination combination had any effect. Tr. 447-48. He testified "I don't think that the combination of DT and hepatitis B changes my opinion about causation at all . . . whether they're together or separate doesn't make any difference to me." Tr. 404.

Dr. Sladky also stated Mr. Contreras's Td vaccination did not have any effect on his condition. He was unaware of any research that measured the effect, if any, a combination of the hepatitis B and Td vaccines has. Tr. 359-60. He opined that the interval between Mr. Contreras's hepatitis B and Td vaccinations and the onset of his transverse myelitits "was implausibly short to invoke causality." Exhibit P at 4.

(4) Adjuvant

Apart from the possible role of the Td vaccine as an adjuvant, there was no discussion about the adjuvant contained within the hepatitis B vaccine, alum, in the pre-trial disclosures. Dr. Poser did not mention alum in his reports. See exhibits 22 and 23. Dr. Steinman similarly did not discuss alum in his reports. See exhibits 55 and 124. Likewise, Dr. Steinman did not testify about alum during his testimony from April 19-20, 2010.

However, during his testimony on July 28, 2011, Dr. Steinman raised the idea that alum could have contributed to Mr. Contreras's alleged quick reaction. He testified that the adjuvant "alum" in the Td vaccine "is a very powerful stimulator of . . . the inflammosome." Tr. 620. In his opinion, the alum adjuvant explains, in part, why Mr. Contreras had a 24-hour reaction to his vaccines. Tr. 621.

Although Dr. Whitton agreed that "[t]here is little doubt that adjuvants do enhance the adaptive immune system," Tr. 654, he disagreed with Dr. Steinman's opinion that the alum adjuvant could have caused Mr. Contreras to develop transverse myelitis within 24 hours. He opined that it was "[a]bsolutely not" possible. Tr. 655. He described adjuvants as providing "a more powerful springboard for the adaptive response." Tr. 654. He explained that "an adjuvant does not necessarily accelerate the [immune system's] adaptive response . . . [b]ut rather it enhances the degree to which the adaptive immune response subsequently develops." Tr. 656.

(5) Prior Exposure to Epstein-Barr Virus and mycoplasma pneumonia

The parties do not dispute that Mr. Contreras had been exposed to the Epstein-Barr Virus (EBV) and mycoplasma pneumoniae prior to his vaccinations. See exhibit 7 at 1026 (documenting Mr. Contreras's EBV infection); id. at 1018 (documenting Mr. Contreras's exposure to mycoplasma pneumoniae). They do, however, dispute whether either had any role in causing or exacerbating Mr. Contreras's condition.

The EBV and, to a lesser extent, mycoplasma pneumoniae have been considered antecedent infections that might cause transverse myelitis (and GBS). See, e.g., exhibit 145 (Rafael L. Ufret-Vincentry, In Vivo Survival of Viral Antigen-specific T Cells that Induce Experimental Autoimmune Encephalomyelitis, 188(9) J. Experimental Med. 1725 (1998)); see also Tr. 524-26.

Dr. Steinman considered Mr. Contreras's EBV infection to be a possible explanation for why he reacted the way he did to his vaccines. Tr. 148. According to Dr. Steinman, the EBV "could have broken [Mr. Contreras's] tolerance to a myelin protein." Tr. 148. He opined that he and his colleagues "demonstrated . . . that an immune response to Epstein Barr virus can break tolerance to myelin proteins at both the T cell and the antibody level." Exhibit 55 at 2. Simply put, Dr. Steinman opined that Mr. Contreras's previous EBV infection could have made him more vulnerable to developing neurological complications in response to his hepatitis B vaccination. Tr. 204.

In his reports, Dr. Steinman very briefly discussed the relevance of Mr. Contreras's prior exposure to mycoplasma pneumoniae. See exhibit 55 at 2; exhibit 124 at 2. He stated that mycoplasma pneumoniae was "associated with [Mr. Contreras's] diagnosis," exhibit 55 at 2, but he did not expound on this issue in his reports. He stated at the hearing that "mycoplasma [pneumoniae] . . . [is] another microbe that can cause a cross reaction and lead to demyelination," Tr. 149, and can cause GBS. Tr. 150. However, Dr. Steinman stated that it was unknown whether Mr. Contreras's exposure to mycoplasma pneumoniae played a role in his condition because it was indeterminable when Mr. Contreras was exposed to it. Tr. 150-51.

Dr. Poser opined that Mr. Contreras's prior mycoplasma pneumoniae and EBV exposures were "of no clinical significance." Exhibit 22 at 3, ¶ 3. He stated that these infections are "commonly found in the normal American population." Id.

Dr. Sladky opined that Mr. Contreras's exposures to EBV and mycoplasma pneumoniae were "felt to be incidental and consistent with prior exposure." Exhibit A at 2. Dr. Sladky opined that Mr. Contreras's previous EBV exposure played no role in his condition. Tr. 301. As he explained, it is an "a virtually ubiquitous virus." Tr. 301. Further, he disagreed with Dr. Steinman's contention that EBV sensitizes an individual's immune system. See Tr. 303.

Likewise, Dr. Whitton opined that Mr. Contreras's exposure to EBV played no role in his condition. See exhibit L at 2; Tr. 489. He stated that there was no evidence to support Dr. Steinman's contention that EBV "primed" Mr. Contreras's immune system. Tr. 488-89. Dr. Whitton acknowledged Mr. Contreras's prior exposure to mycoplasma pneumoniae, but did not comment on its relevance. See exhibit L at 2.

None of the experts discussed the relevance of Mr. Contreras's mycoplasma pneumoniae infection aside from Dr. Steinman stating that it can cause GBS, among other neurological complications. However, he did not opine as to whether Mr. Contreras's mycoplasma pneumoniae exposure had any relevance to his condition.

Only Dr. Steinman opined that Mr. Contreras's EBV infection played a role in his condition. Dr. Steinman suggested that Mr. Contreras's EBV infection may have played a role more important than suggested by either Dr. Poser or Dr. Sladky. Dr. Steinman asserted that Mr. Contreras's exposure to EBV made him more vulnerable to an adverse reaction and more vulnerable to a faster adverse reaction. See exhibit 55 at 3; Tr. 148, 155-56, 536.

The problem with Dr. Steinman's theory regarding a potential contributory causative role for EBV is that EBV is very common. If previous exposure to EBV contributed to the hepatitis B vaccine causing demyelinating diseases, then many more people would be suffering from GBS or transverse myelitis. Millions of people have both received the hepatitis B vaccine and been infected with EBV. Yet, diseases like transverse myelitis remain relatively rare. Dr. Poser's opinion that Mr. Contreras's earlier EBV infection carried "no clinical significance" is more persuasive than Dr. Steinman's suggestion.

5. Overall Finding

The Entitlement Decision found that a one-day interval between vaccination and the onset of neurologic problems was too quick to infer causation. The decision stated:

> The Secretary's position is that one day is "simply not plausible," Resp't Br. at 25, and the evidence supports this conclusion. The testimony of Dr. Sladky and Dr. Whitton was consistent with medical literature that shows that, at a minimum, the blood brain barrier would prevent an immune-mediated reaction in the spinal cord in one day. Dr. Whitton did not see this case as being one that falls within a shade of grey. For Dr. Whitton, "24 hours is well into the black." Tr. 478. His opinion is that "there is no credible hypothesis that would explain a 24-hour time-frame, which would tie a vaccine causally to the induction of such a profound central nervous system disease." Tr. 451.

2012 WL 1441315, at *23. On review, the Court expressed concern that the undersigned was requiring scientific certainty and invited a reassessment of whether the evidence is as "black and white as Dr. Whitton asserted." 107 Fed. Cl. at 307.

As part of the remand, the undersigned has again reviewed the evidence including opinions from Dr. Wagner, Dr. Garrett, Dr. Cheung, Dr. Poser, Dr. Steinman, Dr. Sladky, and Dr. Whitton.[51] In analyzing the record, the undersigned has attempted to focus as much as possible upon the evidence of record.[52] The undersigned remains persuaded that a one-day interval is an extreme case, outside of the shades of grey to which Dr. Whitton referred.

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[51] The analysis in the text does not rely upon Dr. Sladky's opinion extensively. Thus, under the circumstances in which the Secretary presented the opinion of a different doctor, the problems in Dr. Sladky's licensing and the non-disclosure of these problems has minimal effect on this case.

[52] Of course, it would be naïve to say that the undersigned's experience as a special master in reading reports from experts, reviewing medical literature submitted by the parties, listening to testimony from experts, and reading decisions written by other special masters played no part in how the evidence was analyzed. It would seem nearly impossible to unlearn what these experiences have taught. Moreover, it seems that special masters are to use their "accumulated expertise" in determining whether a petitioner is entitled to compensation. Hodges v. Sec'y of Health & Human Servs., 9 F.3d 958, 961 (Fed. Cir. 1993).

The original decision cited cases in which other special masters had discussed the minimal time-frame for an immune-mediated reaction. These decisions were cited because of the persuasiveness of their reasoning. 2012 WL 1441315, at *24.

Since the April 5, 2012 Entitlement Decision, additional cases appear to support the finding that a one-day interval is too quick to infer causation. Mohamud v. Sec'y of Health & Human Servs., No. 09-812V, 2013 WL 5314611, at *15 (Fed. Cl. Spec. Mstr. Aug. 30, 2013)

(... continued)

Mr. Contreras's claim that 26 hours is a medically acceptable time for an autoimmune-medicated reaction in his spinal cord is comparable to a claim that a person can drive from Washington, DC to Los Angeles, CA in one day. Evaluating such a claim requires some knowledge about the distance between the two geographic locations, the roads connecting those locations, the variety of automobiles, and the maximum speed of available automobiles. Given the relatively common experience in driving, few (if any) people would accept an opinion that it is possible to drive coast to coast in one day.

Here, although the medical principles are less known to the world at-large, immunologists such as Dr. Whitton understand how long biologic processes take. He has persuasively explained the relevant immunologic principles. The undersigned's experience informs my conclusion that Dr. Whitton is likely to be correct. Conversely, Mr. Contreras's group of experts, led by Dr. Steinman, have not presented a persuasive explanation for the opinion that the administration of a vaccine can cause an otherwise healthy person to develop transverse myelitis is just 26 hours.

Furthermore, Mr. Contreras's list of proposed accelerants, such as past immunizations and his Hispanic ancestry, do not persuasively show why what is usually a many day process could happen in about one day. To continue the analogy to driving cross-country, Mr. Contreras's proposals are like suggestions to take one highway and not another highway, or to employ more than one driver. While these suggestions could shorten the cross-country trip, they do not alter the fundamental fact that the trip is more than 2,000 miles. The time to travel this distance by car exceeds one day.

The undersigned is mindful that Mr. Contreras's burden is merely a preponderance of the evidence and not scientific certainty. See Hodges 9 F.3d at 961-62. Even under the lower standard, Mr. Contreras has not presented persuasive evidence that one day "is medically acceptable to infer causation-in-fact." 107 Fed. Cl. at 303. Consequently, his case fails the third prong of Althen.

(finding preponderant evidence did not support petitioner's argument that an autoimmune reaction via molecular mimicry could manifest in 24 hours, "the timing is too short"); Flores v. Sec'y of Health & Human Servs., No. 10-489V, 2013 WL 5587390, at *10, 18-19 (Fed. Cl. Spec. Mstr. Sept. 12, 2013) (finding that one day between vaccination and onset of symptoms weighed against finding that the vaccine caused the problems). In another case, Dr. Steinman testified that "the medically accepted time frame for the onset of post-vaccinal transverse myelitis would be a few weeks." See Dillon v. Sec'y of Health & Human Servs., No. 10-805V, 2013 WL 3745900, at *9 (Fed. Cl. Spec. Mstr. June 25, 2013).

In light of the Court's concerns about reliance on other cases, see Opinion and Order, 107 Fed. Cl. at 308, the undersigned has attempted not to let any of these decisions influence the outcome of Mr. Contreras's case.

D. Althen Prong Two

The remaining prong from Althen is the second prong, which provides that a petitioner must present preponderant evidence "showing that the vaccination was the reason for the injury." 418 F.3d at 1278. This prong often comes into play when a petitioner has already established that the vaccine can cause an injury (prong one) and the injury arose in a medically acceptable time (prong three). Even when the petitioner has met these two required elements, the petitioner still must establish the second prong of Althen because this element "is not without meaning." Capizzano, 440 F.3d at 1327. The Federal Circuit has acknowledged that, sometimes, the receipt of a vaccine is coincidental to a subsequent disease. Id. at 1327.

The Federal Circuit has identified several factors that may be probative with respect to petitioner's burden on this prong. These include, among other things, the opinions of a petitioner's treating physicians, expert testimony, challenge-rechallenge, pathological markers, and general acceptance. See Capizzano, 440 F.3d at 1322.

1. Statements of Treating Doctors

Dr. Garrett stated that Mr. Contreras's transverse myelitis was possibly idiopathic, and also "potentially" vaccine-related. Dr. Garrett's assertion that Mr. Contreras's transverse myelitis was "potentially" vaccine-related implies that the hepatitis B vaccine can cause transverse myelitis. Even if there were a reliable basis for finding that the hepatitis B vaccine "can cause" transverse myelitis, Dr. Garrett's logic is: the hepatitis B vaccine can cause transverse myelitis, the timing in Mr. Contreras's case is acceptable, and other potential causes do not exist; therefore, Mr. Contreras's hepatitis B vaccine did, in fact, cause his transverse myelitis. When presented with this reasoning from a specially retained expert (not a treating doctor), the Federal Circuit rejected this logic in Moberly. See Moberly, 592 F.3d at 1323.

As discussed, only Dr. Garrett and Dr. Wagner considered Mr. Contreras's condition to be vaccine-related. See generally section V.B.3.a), above. None of his many other treating doctors stated that his vaccinations caused his transverse myelitis. In fact, in response to his parents' questioning whether Mr. Contreras's vaccines could have caused his injuries, Dr. Babbitt explained to his parents that "there is no clear medical literature to support anything other than association" between transverse myelitis and his vaccines. Exhibit 7 at 126. Dr. Cheung and Dr. Lake also explained to Mr. Contreras's parents that the vaccines did not cause their son's illness. Id.

2. Potential Alternative Causes

A petitioner is "permitted to use evidence eliminating other potential causes to help carry the burden on causation." Walther v. Sec'y of Health & Human Servs., 485 F.3d 1146, 1151 (Fed. Cir. 2007). "[T]he exclusion of alternative etiologies is usually quite probative with respect to prong two of the Althen analysis—i.e., whether the vaccine caused the injury in a particular case," Caves, 100 Fed. Cl. at 144. This is permissible even when the alleged injury may have an idiopathic (unknown) cause in some instances. Pafford, 451 F.3d at 1357-59. Special masters may not require petitioners to eliminate all possible alternative causes to meet

their burden on causation, Stone v. Sec'y of Health & Human Servs., 676 F.3d 1373, 1380 (Fed. Cir. 2012), but evidence that eliminates other alternative causes must be considered in assessing whether they have satisfied their burden. Doe v. Sec'y of Health & Human Servs., 601 F.3d 1349, 1358 (Fed. Cir. 2010).

The April 5, 2012 Entitlement Decision did not address Mr. Contreras's argument that other known potential causes of transverse myelitis had been ruled out because the Entitlement Decision did not reach prong 2. See 2012 WL 1441315 at *24. On review, the Court noted that the Entitlement Decision had no "finding . . . as to whether or not [Mr. Contreras] successfully ruled out alternative causes for [his] illness, and . . . [the court could not] determine whether such a finding would have aided [Mr. Contreras] in meeting his burden." Opinion and Order, 107 Fed. Cl. at 296. For this reason, the Court held that the decision on remand should consider whether alternative etiologies have been ruled out. Id. at 296-97.

Throughout this litigation, Mr. Contreras has maintained that potential alternative causes for his neurologic problem have been excluded. E.g. Pet'r Pre-hearing Br. at 23; Pet'r Post-hearing Br. at 23. He presents the same argument in his most recent briefs. See Pet'r Br. on Remand 19-21; Pet'r Remand Reply at 1-4.

As to whether there is a known alternative potential cause for Mr. Contreras's transverse myelitis, there is no factual dispute. Dr. Sladky did not identify any alternative causes. Tr. 351; see also exhibit I at 1. Dr. Whitton did not identify any alternative causes. See exhibit N at 1. The Secretary did not argue that she had introduced any evidence suggesting an alternative cause. See Resp't's Br. on Remand at 26; Resp't's Post-Hearing Br.

Where the parties differ is in the significance of a finding that all known potential causes for transverse myelitis have been excluded. Mr. Contreras contends that this elimination of identifiable alternative causes of his TM bolsters his claim that it is vaccine-related. See, e.g., Pet'r's Pre-Trial Br. at 23.

As suggested by the foregoing citations, Federal Circuit precedent is not entirely clear about the consequence of ruling out other possible alternative causes. Compare Walther, 485 F.3d at 1151, with Moberly, 592 F.3d at 1323.

In cases in which a petitioner has established that the vaccine can cause the injury and the injury arose in the correct time, the exclusion of other factors may be probative that the vaccine caused the injury. A prerequisite is that the petitioner must establish, on a more likely than not basis, that the vaccine can cause the injury. See Tamraz v. Lincoln Elec. Co., 620 F.3d 665, 674 (6th Cir. 2010); Hendrix ex rel. G.P. v. Evenflo Co., Inc., 609 F.3d 1183, 1197–98 (11th Cir. 2010) (affirming district court's exclusion of expert's opinion because the doctor "'fail[ed] to show how, by 'scientifically valid methodology' traumatic brain injury could ever be a possible cause of autism in anyone") (citation omitted); Ruggiero v. Warner-Lambert Co., 424 F.3d 249, 254 (2d Cir. 2005) (affirming trial court's exclusion of an expert's opinion on the ground that the opinion was not reliable according to the Daubert standard).

In contrast, the exclusion of other potential factors does not promote the finding that the vaccine can cause the injury, which is the inquiry in prong one. See Caves, 100 Fed. Cl. at 144; Veryzer v. Sec'y of Health & Human Servs., 100 Fed. Cl. 344, 355-56 (2011). The fact that Mr. Contreras did not display any symptoms of being infected with a virus within the three weeks before his transverse myelitis began supports the view that a virus did not cause his transverse myelitis. But, the fact that a virus did not cause transverse myelitis does not mean that the hepatitis B vaccine caused the transverse myelitis. Fadelalla v. United States, 45 Fed. Cl. 196, 201 (1999) ("[t]he absence of an alternative cause does not relieve petitioner of her duty affirmatively to demonstrate by a preponderance of the evidence that the rubella vaccine more likely than not caused her injury. . . . Petitioner cannot rely on the fact that respondent's expert failed to prove the cause of petitioner's GBS as a substitute for petitioner's own failure of proof of causation-in-fact").

As explained in section B, Mr. Contreras has not established, by a preponderance of evidence, that the hepatitis B vaccine can cause transverse myelitis via molecular mimicry. As explained in section C, even if molecular mimicry were a persuasive theory, Mr. Contreras has not established that the timing is medically acceptable. In light of these findings, it becomes impossible to find that there is a logical sequence of cause and effect between the hepatitis B vaccination and Mr. Contreras's transverse myelitis. See Capizzano, 440 F.3d at 1326.

A finding that Mr. Contreras did not establish that the hepatitis B vaccination was a cause of his transverse myelitis means that something else caused the disease. This implication is acceptable to the Federal Circuit. In Bazan, the Federal Circuit explained: "It is certainly true that a finding that the administration of a vaccine was not a cause-in-fact of an injury necessarily implies that some other cause resulted in the injury." 539 F.3d at 1353. The same result occurs here.[53]

[53] It appeared that the Court of Federal Claims in Caves followed the reasoning that the Federal Circuit offered in Bazan. In Caves, which was another case involving transverse myelitis, the Court offered a thorough explanation of the value of elimination of other potential causes:

> [T]he only situation in which the elimination of alternative causes would prove that the vaccine was in fact the cause of the injury is when all potential causes of the injury are known and all, or at least most, of those causes other than the vaccine have been eliminated. That is not the case here. The experts for both parties agreed that, in the majority of cases of TM, the underlying cause is never known or discovered. See Ex. 29 at 1; Tr. at 51–52, 103. For that reason, while the elimination of alternative causes might marginally increase the likelihood that a vaccine caused an injury, such a showing would be insufficient in most cases to meet the second prong of Althen. Because the majority of cases of TM are idiopathic, in other words, the elimination of other identified

(... continued)

VI. Conclusion

A very condensed account of Mr. Contreras's medical history is that on June 16, 2003, he received booster doses of the tetanus-diphtheria vaccine and the hepatitis B vaccine. The very next day, he developed neurological problems that an MRI located near four vertebrae in his cervical spinal cord. The radiologist interpreting this imaging and Mr. Contreras's treating neurologist diagnosed him as suffering from transverse myelitis.

When the question of whether the vaccines caused Mr. Contreras's transverse myelitis was asked, a specialist in infectious diseases investigated. Dr. Cheung found that although there were some case reports, "there is no proof of causation and several cohort studies have suggested that there is no increased incidence [of demyelinating diseases] following vaccination." Dr. Cheung also found that in the case reports that did associate vaccination and demyelinating diseases, the latency between the two events was "slightly longer" than what happened to Mr. Contreras. Exhibit 7 at 147.

The ensuing litigation has essentially confirmed Dr. Cheung's analysis. Although Mr. Contreras received assistance from an excellent attorney and well-credentialed experts, his proof never rose to a preponderance of the evidence. While his experts drew support from case reports, the Secretary presented epidemiological studies, a stronger form of evidence, that showed that the hepatitis B vaccination is unlikely to cause demyelination.

The collection of case reports is generally consistent with this view because only a single report presents a temporal sequence in which approximately one day passed between a vaccination and the onset of GBS. In the overwhelming majority of other reported cases, the latency period was along the lines of what the Secretary's experts suggested—at least five to seven days.

Further, even if hepatitis B vaccination could cause demyelination, the one-day interval is not a time-frame for which it is medically acceptable to infer causation. Based upon rodent studies, including ones cited by Mr. Contreras's expert, the Secretary's expert persuasively explained that steps in molecular mimicry take multiple days and cannot occur in a single day.

For these reasons, Mr. Contreras has not met his burden of proof and is not entitled to compensation. The Clerk's Office is instructed to enter judgment in accord with this decision

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> causes would have limited probative value in establishing the influenza vaccine as the actual cause of petitioner's TM.

Caves, 100 Fed. Cl. at 141.

While the Opinion and Order characterizes this discussion as dicta,107 Fed. Cl. at 298 n.30, the reasoning in Caves seems apt for Mr. Contreras's case.

unless a motion for review is filed. The Clerk's Office is also instructed to provide this decision to the presiding judge pursuant to Vaccine Rule 28.1(a).

IT IS SO ORDERED.

s/Christian J. Moran
Christian J. Moran
Special Master