IN THE UNITED STATES COURT OF FEDERAL CLAIMS
OFFICE OF SPECIAL MASTERS

No. 10-261V
Filed: June 21, 2013
For Publication

JEFFREY TOMPKINS, as personal representative of the estate of William Bruce Tompkins, deceased, Petitioner,	*	Guillain-Barré Syndrome; GBS; Upper Respiratory Infection; IOM Reports; Alternate Cause; Timing; Non-Table Vaccines; Tetanus Vaccine; Case Reports; VAERS Data and Research
v.	*	
SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES, Respondent.	*	

Stephen Leshner, Esq., Stephen I. Leshner, P.C., Phoenix, AZ, for petitioner.
Lisa Watts, Esq., U.S. Dept. of Justice, Washington, DC, for respondent.

DECISION[1]

Vowell, Special Master:

On April 28, 2010, Mr. William Tompkins ["William"] timely filed a petition for compensation under the National Vaccine Injury Compensation Program, 42 U.S.C. §300aa-10, *et seq*.[2] [the "Vaccine Act" or "Program"] alleging that vaccinations he received on July 23 and August 22, 2008, caused him to develop Guillain-Barré syndrome ["GBS"].[3] Petition, ¶¶ 3, 5, 9.

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[1] Because this decision contains a reasoned explanation for the action in this case, I intend to post this decision on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, § 205, 116 Stat. 2899, 2913 (codified as amended at 44 U.S.C. § 3501 note (2006)). In accordance with Vaccine Rule 18(b), petitioner has 14 days to identify and move to delete medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, I agree that the identified material fits within this definition, I will delete such material from public access.

[2] National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755. Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2006).

[3] Guillain-Barré syndrome is a "rapidly progressive ascending motor neuron paralysis." DORLAND'S ILLUSTRATED MEDICAL DICTIONARY (32nd ed. 2012) ["DORLAND'S"] at 1832. Its presentation and causes are discussed in more detail in Section IV.B below.

In order to prevail under the Program, a petitioner must prove either a "Table" injury[4] or that a vaccine listed on the Table was the cause in fact of an injury (an "off-Table" injury). Because GBS is not a Table injury for any vaccine appearing on the Vaccine Injury Table, petitioner must produce preponderant evidence that a covered vaccine is responsible for William's injury. After considering the record as a whole,[5] I hold that petitioner has failed to produce such evidence.

The medical facts are largely uncontested. William received several vaccines that are covered by the Vaccine Act in the five weeks prior to the onset of GBS symptoms, but he also received two vaccines not covered by the Act.[6] Additionally, William first sought treatment for symptoms of an upper respiratory illness two weeks (16 days) before onset of his GBS symptoms.

The only factual issue that appears to be in dispute is whether William was acutely ill at the time of the second set of vaccinations. Petitioner's expert, Dr. Steven Pike, asserts that William was acutely ill with an upper respiratory infection with fever at that time. According to Dr. Pike, the vaccinations, in conjunction with William's illness, caused him to develop GBS The evidence does not support his assertion that William was acutely ill and it is inadequate to demonstrate that any of the vaccines that William received can cause GBS, much less that they did so in this case.

Respondent asserts that the antecedent respiratory infection itself was the most likely cause of William's GBS. I find that his upper respiratory infection, which began two weeks prior to the onset of his GBS symptoms, is a well-recognized cause of GBS,

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[4] A "Table" injury is an injury listed on the Vaccine Injury Table, 42 C.F.R. § 100.3 (2011), corresponding to the vaccine received within the time frame specified.

[5] *See* § 13(a): "Compensation shall be awarded . . . if the special master or court finds on the record as a whole–(A) that the petitioner has demonstrated by a preponderance of the evidence the matters required in the petition by section 300aa-11(c)(1);" *see also* § 13(b)(1) (indicating that the court or special master shall consider the entire record in determining if petitioner is entitled to compensation).

[6] The adult pneumococcal vaccine, which was administered on July 23, 2008, and the yellow fever vaccine, which was administered on August 22, 2008 (Petitioner's Exhibit ["Pet. Ex."] 1, pp. 3-4), are not vaccines covered by the Vaccine Act. *See* 42 C.F.R. § 100.3. Children are administered a pneumococcal conjugate vaccine (Prevnar) while adults receive pneumococcal polysaccharide vaccines (Pneumovax). *See* http://www.cdc.gov/vaccines/vpd-vac/pneumo/default.htm (last visited June 20, 2013). Although the childhood formulation of the pneumococcal vaccine appears on the Vaccine Injury Table, the adult formulation does not. 42 C.F.R. § 100.3; *see also Schmidt v. Sec'y, HHS*, No. 11-410V, 2011 WL 6148590, at *2 (Fed. Cl. Spec. Mstr. Nov. 21, 2011); *Morrison v. Sec'y, HHS,* No. 04-1683V, 2005 WL 2008245, at *2 (Fed. Cl. Spec. Mstr. July 26, 2005); *Finley v. Sec'y, HHS*, No. 04-874V, 2004 WL 2059490, at *2 (Fed. Cl. Spec. Mstr. Aug. 24, 2004) (finding that pneumococcal polysaccharide vaccines are not covered under the Vaccine Program).

occurred at an appropriate temporal interval before onset of symptoms, and is the most likely cause for William's GBS. I therefore hold that petitioner failed to establish vaccine causation by preponderant evidence and the petition is dismissed.

I. Procedural History.

Initially, this case proceeded along a settlement track, with the parties reaching a tentative litigative risk settlement in October, 2010. Before the settlement was finalized, William died of injuries sustained in an automobile accident.[7] Rather than execute the settlement agreement, respondent moved to dismiss the case, asserting that William's death deprived this court of jurisdiction over his vaccine injury claim.[8] Petitioner's counsel opposed the motion to dismiss and sought to substitute William's father, Mr. Jeffrey Tompkins, who had been appointed the personal representative of William's estate, as petitioner.

In an unpublished ruling filed on October 25, 2011, Special Master Gary Golkiewicz denied respondent's motion to dismiss and granted the motion to substitute Mr. Jeffrey Tompkins as the petitioner on behalf of his late son's estate.[9] Thereafter, the case proceeded as a contested matter.

On January 5, 2012, respondent filed a Vaccine Rule 4 report and an expert report by Dr. Daniel M. Feinberg. Doctor Feinberg's report responded to the expert report of Dr. Pike, which, along with William's medical records, had been filed with the petition. Petitioner filed a supplemental expert report from Dr. Pike on January 30, 2012, and respondent filed a supplemental report by Dr. Feinberg in answer on March 15, 2012. This case was thereafter set for a July 17, 2012 hearing.

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[7] Petitioner has conceded that William's death was unrelated to his alleged vaccine injury. *See* Petitioner's Response to Respondent's Motion to Dismiss, filed Jun. 10, 2011, at 2; Pet. Ex. 11 (death certificate), filed as Exhibit A to Motion to Substitute Petitioner on Apr. 14, 2011.

[8] The settlement agreement expressly provided that the agreement was voidable by either party if petitioner died before entry of judgment. *See* Stipulation, filed Apr. 14, 2011, as Exhibit B to Petitioner's Statement of Damages Sought, at ¶ 14. Respondent exercised her option. *See* Motion to Dismiss, filed May 16, 2011, at 1 n.1. The settlement agreement itself was filed over respondent's objections. *Id*., at 1-2 n.1.

[9] In so ruling, Special Master Golkiewicz relied heavily on my ruling in *Sanders*, a case that presented nearly identical issues. *Sanders v. Sec'y, HHS*, No. 99-430V, 2009 WL 1759452 (Fed. Cl. Spec. Mstr. May 27, 2009). I do not revisit Special Master Golkiewicz's ruling in this decision. The Federal Circuit has recently stated that the right of the estate of a vaccine-injured individual to pursue a claim filed prior to death is well recognized. *Figueroa v. Sec'y, HHS,*--- F.3d ---, 2013 WL 1811018, at *3, *7 (Fed. Cir. May 1, 2013).

Special Master Golkiewicz's impending retirement necessitated the reassignment of the case to me on May 7, 2012. At the entitlement hearing in Phoenix, AZ on July 17, 2012, Drs. Pike and Feinberg were the only witnesses. Post-hearing briefs were waived. The issues are now ripe for a ruling on the issue of entitlement.

II. Legal Standards Applying to Off-Table Causation Cases.

When a petitioner alleges an off-Table injury, eligibility for compensation is established when, by a preponderance of the evidence, petitioner demonstrates that he received, in the United States, a vaccine set forth on the Vaccine Injury Table ["Table"] and sustained an illness, disability, injury, or condition caused by the vaccine or experienced a significant aggravation of a preexisting condition. He must also demonstrate that the condition has persisted for more than six months.[10] Vaccine litigation rarely concerns whether the vaccine appears on the Table, the situs for administration, or whether the symptoms have persisted for the requisite time. In most Vaccine Act litigation, the issue to be resolved by the special master is whether the injury alleged was caused by the vaccine.

To establish legal cause in an off-Table case, Vaccine Act petitioners must establish each of the three *Althen* factors by preponderant evidence: (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 proximate temporal relationship between vaccination and injury. *Althen v. Sec'y, HHS,* 418 F.3d 1274, 1278 (Fed. Cir. 2005); *see de Bazan v. Sec'y, HHS*, 539 F.3d 1347, 1351-52 (Fed. Cir. 2008); *Caves v. Sec'y, HHS,* 100 Fed. Cl. 119, 132 (2011), *aff. per curiam*, 463 Fed. Appx. 932, 2012 WL 858402 (Fed. Cir. 2012) (specifying that each *Althen* factor must be established by preponderant evidence). The applicable level of proof is the "traditional tort standard of 'preponderant evidence.'" *Moberly v. Sec'y, HHS*, 592 F.3d 1315, 1322 (Fed. Cir. 2010) (citing *de Bazan*, 539 F.3d at 1351; *Pafford v. Sec'y, HHS*, 451 F.3d 1352, 1355 (Fed. Cir. 2006); *Capizzano v. Sec'y, HHS*, 440 F.3d 1317, 1320 (Fed. Cir. 2006); *Althen,* 418 F.3d at 1278). The preponderance standard "requires the trier of fact to believe that the existence of a fact is more probable than its nonexistence." *In re Winship*, 397 U.S. 358, 371 (1970) (Harlan, J., concurring) (internal quotation and citation omitted).

Another formulation of the causation requirement in off-Table cases is the "Can it cause?" and "Did it cause?" inquiries used in toxic tort litigation. These queries are also

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[10] Section 13(a)(1)(A). This section provides that petitioner must demonstrate "by a preponderance of the evidence the matters required in the petition by section 300aa–11(c)(1) . . . ." Section 11(c)(1) contains the factors listed above, along with others not relevant to this case.

referred to as issues of general and specific causation. Prong 1 of *Althen* has been characterized as an alternative formulation of the "Can it cause?" or general causation query. Prong 2 of *Althen*, the requirement for a logical sequence of cause and effect between the vaccine and the injury, has been characterized as addressing the "Did it cause?" or specific causation query. *See Pafford v. Sec'y, HHS*, No. 01-165V, 2004 WL 1717359, at *4 (Fed. Cl. Spec. Mstr. July 16, 2004), *aff.*, 64 Fed. Cl. 19 (2005), *aff.*, 451 F.3d 1352. The third *Althen* factor is subsumed into the other inquiries. Even if a particular vaccine has been causally associated with an injury, petitioner must still establish facts and circumstances that make it more likely than not that this vaccine caused his particular injury. Timing may be one of those circumstances.

Whether a case is analyzed under *Althen* or the "Can it cause?" formulation, petitioners are not required to establish identification and proof of specific biological mechanisms, as "the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body." *Althen*, 418 F.3d at 1280. The petitioner need not show that the vaccination was the sole cause, or even the predominant cause, of the injury or condition; showing that the vaccination was a "substantial factor"[11] in causing the condition and was a "but for" cause are sufficient for recovery. *Shyface*, 165 F.3d at 1352; *see also Pafford,* 451 F.3d at 1355 (petitioner must establish that a vaccination was a substantial factor and that harm would not have occurred in the absence of vaccination). Petitioners cannot be required to show "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." *Capizzano*, 440 F.3d at 1325. Causation is determined on a case by case basis, with "no hard and fast *per se* scientific or medical rules." *Knudsen v. Sec'y, HHS,* 35 F.3d 543, 548 (Fed. Cir. 1994). Close calls regarding causation must be resolved in favor of the petitioner. *Althen*, 418 F.3d at 1280; *but see Knudsen*, 35 F.3d at 550 (when evidence is in equipoise, the party with the burden of proof fails to meet that burden).

In Vaccine Act cases, special masters are frequently confronted by expert witnesses with diametrically opposed positions on causation. When experts disagree, many factors influence a fact-finder to accept some testimony and reject other contrary testimony. As the Federal Circuit noted, "[a]ssessments as to the reliability of expert

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[11] The Restatement (Third) of Torts has eliminated "substantial factor" in the factual cause analysis. § 26 cmt. j (2010). Because the Federal Circuit has held that the causation analysis in the Restatement (Second) of Torts applies to off-Table Vaccine Act cases (*see Walther v. Sec'y, HHS*, 485 F.3d 1146, 1151 (Fed. Cir. 2007); *Shyface v. Sec'y, HHS*, 165 F.3d 1344, 1352 (Fed. Cir. 1999)), this change does not affect the determination of legal cause in Vaccine Act cases: whether the vaccination is a "substantial factor" is still a consideration in determining whether it is the legal cause of an injury.

testimony often turn on credibility determinations, particularly in cases . . . where there is little supporting evidence for the expert's opinion." *Moberly*, 592 F.3d at 1325-26. Objective 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.

By specifying petitioners' burden of proof in off-Table cases as the preponderance of the evidence, directing special masters to consider the evidence as a whole, and stating that special masters are not bound by any "diagnosis, conclusion, judgment, test result, report, or summary" contained in the record (§13(b)(1)), Congress contemplated that special masters would weigh and evaluate opposing expert opinions in determining whether petitioners have met their burden of proof.[12] In weighing and evaluating expert opinions in Vaccine Act cases, the same factors the Supreme Court has considered important in determining their admissibility provide the weights and counterweights. *See Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 149-50 (1999); *Terran v. Sec'y, HHS*, 195 F.3d 1302, 1316 (Fed. Cir. 1999). As the Supreme Court has noted, a trial court is not required to accept the *ipse dixit* of any expert's medical or scientific opinion, because the "court may conclude that there is simply too great an analytical gap between the data and the opinion proffered." *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997).

Although *Daubert v. Merrell Dow Pharmaceuticals*[13] interpreted Federal Rule of Evidence 702, an evidentiary rule not applicable to Vaccine Act cases, *Daubert* nevertheless provides a useful framework for evaluating scientific evidence in Program cases. *Terran*, 195 F.3d at 1316 (concluding it was reasonable for the special master to use *Daubert* to evaluate the reliability of an expert's testimony); *Cedillo v. Sec'y, HHS,* 617 F.3d 1328, 1339 (Fed. Cir. 2010) (noting that special masters are to consider all relevant and reliable evidence filed in a case and may use *Daubert* factors in their evaluation of expert testimony); *Davis v. Sec'y, HHS*, 94 Fed. Cl. 53, 67 (2010) (describing the *Daubert* factors as an "acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted . . . by special masters in vaccine cases"); *see also Snyder v. Sec'y, HHS*, 88 Fed. Cl. 706, 718 (2009) quoting *Ryman v. Sec'y, HHS*, 65 Fed. Cl. 35, 40-41 (2005) (special masters perform gatekeeping function when determining "whether a particular petitioner's expert medical

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[12] *See* § 13(a)(1)(A) (preponderance standard); § 13(a)(1) ("Compensation shall be awarded . . . if the special master or court finds on the record as a whole . . . ."); § 13(b)(1) (indicating that the court or special master shall consider the entire record in determining if petitioner is entitled to compensation and special master is not bound by any particular piece of evidence).

[13] 509 U.S. 579 (1993).

testimony supporting biological probability may be admitted or credited or otherwise relied upon" and as a "trier-of-fact [a special master] may properly consider the credibility and applicability of medical theories"). The special master's use of *Daubert's* factors to evaluate the reliability of expert opinions in Vaccine Act cases has been cited with approval by the Federal Circuit more recently in *Andreu v. Sec'y, HHS,* 569 F.3d 1367, 1379 (Fed. Cir. 2009) and *Moberly,* 592 F.3d at 1324; *see also Vaughan v. Sec'y, HHS,* 107 Fed. Cl. 212, 222 (2012) ("The Federal Circuit has repeatedly stated that the Special Master may refer to *Daubert* to assess reliability of expert testimony in vaccine cases."). Special masters decide questions of credibility, plausibility, probability, and reliability, and ultimately determine to which side the balance of the evidence is tipped. *See Pafford*, 451 F.3d at 1359.

Bearing all these legal standards in mind, I turn to the evidence presented in this case.

III. Relevant Medical History.

A. Facts not in Dispute.

William was a healthy 19 year old when he entered the Marine Corps and reported to "boot camp" on July 21, 2008. Pet. Exs. 3, p. 97 (Recruit Screening Examination); 7 at 2 (DD Form 214, reflecting his accession date). He received his first set of routinely administered vaccinations two days later, on July 23, 2008. At that time, William received measles, mumps, and rubella ["MMR"]; hepatitis A and B (administered in a combined "Twinrix" vaccine); pneumococcal; and meningococcal vaccines. Pet. Ex. 1, p. 4.

On August 9, 2008, while still in boot camp, William reported to sick call complaining of a sore throat (which he rated on a pain scale as 7 out of 10), fever, chills, night sweats, headache, earache, and neck stiffness. Pet. Ex. 3, p. 94. He was assessed as having an upper respiratory infection which was treated with some non-prescription medications, including acetaminophen for pain and fever, pseudoephedrine for nasal congestion, and Cepacol lozenges for his sore throat. William continued with recruit training in spite of this illness. *Id.* at 95.

William was seen again on August 15, 2008, for a sore throat and a very painful headache (scoring it 8 out of 10 on a pain scale). He was coughing up sputum, but the night sweats, fever, chills, and neck stiffness had resolved. His throat was inflamed, but his tonsils had no exudate. He was assessed as having an upper respiratory infection with sinus congestion, sore throat, and sinus headache, and prescribed ibuprofen, Mucinex, Claritin-D, and Nasonex. *Id*., pp. 92-93. The latter three medications are used to treat nasal congestion and allergy symptoms. This time William was placed on "sick in quarters" status for 24 hours, followed by 48 hours of light duty. Although he

was told to return to the clinic the following morning for reevaluation, there is no record that he did so. *Id*., p. 93.

On August 22, 2008, William received a second set of vaccinations, which included a second dose of Twinrix, polio, a combined tetanus, diphtheria, and acellular pertussis ["Tdap"],[14] varicella, and yellow fever vaccines. Pet. Ex. 1, pp. 2-3.

William reported to a military primary care clinic on the morning of August 28, 2008, with a chief complaint of numbness and tingling in his extremities that had begun two days earlier with tingling in his fingers and toes. The symptoms progressed to significant weakness, such that he had trouble dressing and walking. Pet. Exs. 2, p. 1; 3, pp. 87-88. This places onset of his symptoms on or about August 26, 2008.[15] He reported feeling terrible, but indicated he had been well previously. Pet. Ex. 3, p. 87. He had no chest congestion or cough, but reported mild dyspnea (shortness of breath). *Id*. He reported no fever, chills, or night sweats. *Id.*

On examination, he had quadriparesis and limb weakness. Pet. Ex. 3, pp. 89-90. In contrast to his examination on August 15, there was no evidence of inflammation in his throat. However, there was ample evidence of muscle weakness: William could not make a fist with either hand, his hand movements were clumsy or awkward, and his arms, shoulders, and both legs were weak. His deep tendon reflexes were absent or diminished. *Id.*

William was transferred from the local base hospital to the Naval Medical Center in San Diego, where he was admitted to the Medical Intensive Care Unit with a probable diagnosis of GBS-Acute Inflammatory Demyelinating Polyneuropathy ["AIDP"].[16] The narrative summary completed for his hospital stay provided some additional details, indicating that he went to the hospital because he was unable to walk to the sick call clinic, even with the assistance of another recruit. The summary reflected that he had received vaccinations about six weeks earlier,[17] had suffered from an upper respiratory

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[14] In his report, Dr. Pike used the abbreviation "TDaP" to refer to this vaccine. I use the abbreviation "Tdap," as that is the abbreviation used in William's vaccination record, Pet. Ex. 1, p. 3.

[15] In his initial expert report, Dr. Pike also indicated that onset of William's GBS occurred on or about August 26, 2008. Pet. Ex. 10 at 10.

[16] AIDP is another term for the type of GBS most common in the United States. P. Haber, et al., *Vaccines and Guillain-Barré Syndrome*, DRUG SAFETY 32(4): 309-23, 311 (2009), filed as Pet. Ex. 36 and Respondent's Exhibit ["Res. Ex."] E. Hereinafter, this review article will be cited as Haber (2009), Pet. Ex. 36.

[17] The August 22, 2008 vaccinations, received four days prior to onset of symptoms, were not mentioned.

infection two weeks earlier, and still had a stuffy nose and cough.[18] Pet. Ex. 2, p. 2. The summary also indicated that William had been transferred to the medical center from the local military hospital based on his symptoms and increasing shortness of breath. *Id*.

William received IVIG[19] treatment for three days while at the medical center. He left the intensive care unit on his fifth day of hospitalization. Pet. Ex. 2, p. 2. However, he remained at the medical center until September 4, 2008, when he was transferred to Continental Rehabilitation Hospital, a rehabilitation facility. *Id.*, pp. 2-3.

William stayed for 30 days at the rehabilitation facility. His discharge summary indicated that some numbness in his fingers and toes remained, and that he still suffered from sinusitis. At the time of his discharge, William was able to jog, walk with a pack, and ride a bicycle, but these activities made him extremely fatigued. Pet. Ex. 3, pp. 140-41.

Upon discharge from the rehabilitation facility on October 6, 2008, William returned to the base hospital where he underwent a medical workup for a Physical Evaluation Board ["PEB"]. The initial medical board evaluation noted that he had made further recovery since his discharge from the rehabilitation facility, but had not returned to baseline and was still "mildly weak." Pet. Ex. 4, p. 2. The weakness prevented him from returning to training. *Id*., p. 3. Consequently, the initial board recommended referral to a formal PEB. *Id.*, p. 4.

On November 20, 2008, the PEB found him unfit for military service based on mild residual deficits from GBS, and placed him on the Temporary Disability Retired List, with a 30% disability rating. Pet. Ex. 5, p. 2. In March 2009, the Department of Veterans Affairs awarded him $243.00 per month in compensation for his service-connected disability. Pet. Ex. 8, p. 6.

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[18] This contrasts with the initial report at the primary care clinic, which twice affirmatively noted "[n]o cough," while noting that William was still able to cough, in spite of his shortness of breath. Pet. Ex. 3, pp. 87-88. Records from the rehabilitation facility to which William was later transferred indicated that he "normally" took Sudafed and Excedrin, suggesting that sinusitis was a recurring or chronic condition. *Id.*, p. 123.

[19] "IVIG" stands for intravenous immunoglobulin. Neil M. Davis, MEDICAL ABBREVIATIONS, 15th Edition, at 178 (2011).

B. Disputed Facts.

In his two reports and during his testimony, Dr. Pike asserted that William was "acutely" ill with an upper respiratory infection on August 22, 2008, when he received his second set of vaccinations. Pet. Exs. 10 at 7; 14 at 14; Tr. at 18, 44. I conclude William was likely experiencing some symptoms of sinusitis and perhaps a lingering cough from his upper respiratory infection at the time of the second set of vaccinations, but there is no evidence that he was acutely ill. I base this conclusion on the following evidence:

1. The second set of vaccines was administered on August 22, 2008, 13 days after William first sought treatment for an upper respiratory infection, and seven days after William was seen and treated for sinusitis and some lingering symptoms of an upper respiratory illness on August 15, 2008. However, when he returned to the health care clinic on August 15, his primary complaint was the sinus headache, which he rated as 8 out of 10 on a pain scale. Although his throat was inflamed, it did not appear infected. He had no fever and was no longer experiencing night sweats or any of the other symptoms he was experiencing on August 9, 2008. Thus, I conclude that William was mostly recovered from his upper respiratory infection, even if he had a painful sinus headache.

2. William experienced sinus problems both prior to and after this upper respiratory illness. He told doctors at the rehabilitation facility that he "normally" took a decongestant and an analgesic for sinusitis, implying that this was a frequent or chronic condition. He continued to have sinus symptoms during the month he spent at the rehabilitation facility. This indicates that his sinus problems were probably not symptomatic of an acute upper respiratory infection.

3. Additional evidence suggests that William was largely recovered from the upper respiratory infection by the time of his August 22 vaccinations. He did not return to the clinic on August 16, 2008, as directed when he was placed on a 24 hour "sick in quarters" status on August 15, 2008. This indicates that the treatment for his sinus problems improved the headache and sore throat such that he did not need further treatment.

4. There are no medical records reflecting any problems between the August 15 visit and his initial GBS symptoms on or about August 26, 2008. There is no indication that he was not participating in boot camp training, a physically and mentally challenging endeavor, at the time of the second set of vaccinations.

5. Although the shot record is the only health record completed during William's immunizations, he was asked for details concerning his prior state of health on August 28, 2008, when he was first seen for his GBS symptoms. He indicated that he had been feeling well prior to developing the numbness and tingling in his extremities. He

specifically denied any recent cough or congestion, indicating that his cold symptoms were gone. Pet. Ex. 3, pp. 87-88. However, at the medical center, he indicated that he had a cough, and that he suffered from sinusitis periodically. He also reported having had a cold about two weeks earlier, implying that it had resolved This, coupled with the report that he had been feeling well prior to onset of his GBS symptoms, suggests that he was not acutely ill at the time of his second set of vaccinations.

IV. Medical Opinions and Other Evidence.

Medically and legally, this is not a difficult case. It appears more complicated than it is because of Dr. Pike's "shotgun" approach to causation and the lack of clarity in his reports and opinions. William's GBS diagnosis is clear and uncontested. Equally clear is the fact that he experienced an upper respiratory infection—the most common antecedent event causally connected to GBS—at precisely the time for his upper respiratory infection and his GBS to be causally associated.

Even if William's antecedent infection alone did not constitute sufficient cause,[20] petitioner's proof never rose to the preponderant evidence standard required by the Vaccine Act for off-Table cases. On each of the days William was vaccinated, he received vaccines covered by the Vaccine Act and vaccines that are not. The receipt of vaccines not covered by the Act is not fatal to a causation case.[21] However, his already weak causation case was further weakened when his own expert testified that yellow fever, a vaccine not covered by the Act, was the vaccine most likely to be causal.

Moreover, neither Dr. Pike's own research nor the medical journal articles filed by petitioner provide adequate support for his causation opinions. The evidence that any covered vaccine that William received could cause GBS is quite weak, and the covered vaccine which Dr. Pike discussed the most, the tetanus component of the Tdap vaccine, was administered too close in time to be causal of William's GBS. Even ignoring the timing issue, the evidence that the tetanus component of the Tdap can cause GBS does not rise to the level of preponderant evidence.

Expert qualifications play a significant role in the weight given to expert opinions, particularly when the opinions expressed are otherwise inadequately supported by

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[20] *See Pafford*, 451 F.3d at 1357-58.

[21] *See Woods v. Sec'y, HHS*, No. 10-377V, 2012 WL 4010485, at *6 (Fed. Cl. Spec. Mstr. Aug. 23, 2012) (finding reasonable basis to file a case where petitioner received a covered and non-covered vaccine); *Walther v. Sec'y, HHS*, No. 00-426V, 2008 WL 243762, at *17 (Fed. Cl. Spec. Mstr. Jan. 14, 2008) (dismissing a claim not because petitioner received both covered and non-covered vaccines, but because the evidence established that the non-covered vaccine was the cause of petitioner's injury).

reliable evidence. *See Moberly*, 592 F.3d at 1325 ("Weighing the persuasiveness of particular evidence often requires a finder of fact to assess the reliability of testimony, including expert testimony, and we have made clear that the special masters have that responsibility in Vaccine Act cases.") (citations omitted).

Petitioner's expert, Dr. Pike, is an emergency physician and medical toxicologist, who relied primarily on case reports and on superseded[22] portions of a 1994 Institute of Medicine ["IOM"] report (filed as Pet. Ex. 26)[23] to opine that William's condition could be the result of all but one of the vaccines he received.[24] Doctor Pike's training in a field other than neurology or immunology and his relative lack of experience in diagnosing and treating GBS, as well as the nature and quality of the evidence that formed the basis for his opinions, were all factors in the weight I gave his opinions regarding vaccine causation.

In contrast, respondent's expert, Dr. Feinberg, is a well-qualified neurologist who diagnoses, treats, and teaches about GBS. He relied upon strong epidemiologic evidence in opining that the most likely cause of William's GBS was his upper respiratory infection. He explained why case reports and VAERS[25] reports, the primary

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[22] The 1994 and 2011 IOM reports are discussed in more detail below, but in summary, the 2011 IOM report changed the conclusions reached in the 1994 IOM report regarding a causal relationship between tetanus vaccine and GBS.

[23] On June 25, 2012, petitioner filed a CD containing all of the references cited in Dr. Pike's reports. Although the other files were readable, the file containing petitioner's exhibit 26 was corrupted. Therefore, I relied on a library copy of the cited reference, K. Stratton, et al., ADVERSE EVENTS ASSOCIATED WITH CHILDHOOD VACCINES: EVIDENCE BEARING ON CAUSALITY (1994) ["1994 IOM Report"], Pet. Ex. 26.

[24] During his testimony, Dr. Pike indicated that he would exclude the hepatitis B vaccine from consideration as causal (Tr. at 10) although his expert reports included it as a possible cause. *See* Pet. Exs. 10 at 7; 14 at 2-3. I thus do not discuss any role this specific vaccine may play in causation.

[25] "VAERS" stands for the Vaccine Adverse Event Reporting System. It is a passive surveillance system in which anyone who thinks a vaccine caused an injury may file a report. In a number of decisions, special masters and judges have concluded that VAERS data is unreliable as the basis for a causation determination in Vaccine Act cases, based on difficulties inherent in the system's design. *See*, *e.g.*, *Capizzano*, 63 Fed. Cl. at 231 (placing limited value on VAERS reports due to the manner in which they are completed); *Analla v. Sec'y, HHS*, 70 Fed. Cl. 552, 558 (2006) (noting VAERS reports offer very little with regard to causality); *Ryman v. Sec'y, HHS,* 65 Fed. Cl. 35, 39-40 (2005) (commenting that VAERS reports tend to be biased toward prevailing concepts of adverse events).

VAERS was intended as a signaling system—a red flag that would trigger more scientifically and medically rigorous examination of the vaccine and the injury flagged. For example, VAERS data signaled an increased risk of intussusception following RotaShield vaccinations, prompting an investigation into a causal association. That investigation prompted the addition of intussusception as a Vaccine Table Injury for the RotaShield vaccine. *Parsley v. Sec'y, HHS,* No. 08-781, 2011 WL 2463539, at *10 (Fed. Cl. Spec.

evidence that formed the basis for Dr. Pike's opinions, are of low quality in making causation assessments.[26] Doctor Feinberg's opinion was enhanced by his candid acknowledgement that the influenza vaccine (which William did not receive), may cause GBS, presumably by the same mechanism by which wild-type influenza infections may set into motion the cascade of events that results in demyelination of peripheral nerves, leading to the neurological symptoms of GBS.

Based on the expert reports, testimony, and supporting literature, as well as upon the "shotgun" approach taken by Dr. Pike vis-à-vis the vaccines responsible and the theories by which they could do so, I conclude that petitioner failed to produce preponderant evidence of vaccine causation. Although molecular mimicry, the primary medical theory advanced, is a possible mechanism of causation,[27] petitioner failed to demonstrate that it is probable for any of the received vaccines that are covered by the Act. His other theories lacked any indicia of reliability. The logical connection between the vaccines and the injury is lacking, based on the timeframes between inciting event

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Mstr. May 27, 2011). *See also* P. Haber, et al., *Guillain-Barré Syndrome Following Influenza Vaccination*, JAMA 292(20): 2478-81 (2004), filed as Pet. Ex. 17 and Res. Ex. D, at 2480 ("Like all passive surveillance systems, VAERS is subject to underreporting, differential reporting, and variability in report quality and completeness. Reporting to VAERS is more likely when the adverse event is severe or occurs shortly after vaccination, the vaccine is newly introduced, and when there has been publicity about a vaccine adverse event."). Hereinafter, this article will be cited as Haber (2004), Pet. Ex. 17.

[26] I note that in his second report, Dr. Pike referred to the assertions made in VAERS reports regarding onset intervals as "facts." Pet. Ex. 14 at 10. While some VAERS reports may be "fact-checked" by a physician who files the report, one of the journal articles filed by respondent (F. Varricchio, et al., *Understanding vaccine safety information from the Vaccine Adverse Event Reporting System*, PEDIATR. INFECT. DIS. J. 23: 287-94 (2004) ["Varricchio"], filed as Res. Ex. J), supports the view that assumptions similar to Dr. Pike's are erroneous: "It is important to understand that submissions to VAERS are not formal case reports, but rather nonstandarized descriptions of symptoms and signs temporally associated with a vaccination or vaccinations. The information in a report is not necessarily complete, nor is it verified in most cases. . . . Follow-up often yields important information. For example investigation of reported deaths determined that the cause of death was significantly different from what originally was stated on the VAERS report in 24% of the cases." *Id*. at 288 (citation omitted). The authors went on to note that "[i]n some media reports and on some websites on the internet, VAERS reports are misrepresented as verified cases of vaccine-caused deaths and injuries." *Id.* at 289.

[27] Taken to extremes, the molecular mimicry theory or any of the other theories Dr. Pike advanced provide a possible explanation for anything to cause or trigger any demyelinating or other autoimmune condition. *See Hennessey v. Sec'y, HHS*, 91 Fed. Cl. 126, 134-35 (2010) (noting Dr. Shoenfeld's broad use of the molecular mimicry theory made it meaningless). However, the theory requires some degree of homology, albeit not perfect homology, between a component of the causal agent and the myelin sheath of the peripheral nerves in order for the immune system to mistake host tissue as an invader. Tr. at 12-14. As the Haber (2009) review article noted, while it is biologically plausible that vaccines, which stimulate the immune system, could lead to GBS by this or other mechanisms, there is little evidence that they do so. Pet. Ex. 36 at 318-19.

and symptoms, the highly tenuous connections between the received vaccines and injury, and the evidence of a far more likely and temporally more appropriate cause. The latter set of vaccinations was administered too close in time to the onset of symptoms to be causal, according to the same IOM Report upon which petitioner relied as evidence for causation.

The reasons for these conclusions are set forth in greater detail below. I begin the analysis of the causation evidence with a comparison of the qualifications of the expert witnesses, followed by a short discussion of GBS. I then summarize Dr. Pike's causation theories and the evidence supporting or refuting those theories and evaluate petitioner's causation case against the *Althen* factors and the *Pafford* "can it cause/did it cause?" inquiry. Although I conclude that the burden never shifted to respondent to prove an alternate cause for William's condition, I examine the evidence supporting an alternate cause for that condition because that alternate cause provides an explanation that is far more likely than Dr. Pike's theories and opinions.

A. Expert Qualifications.

1. Doctor Pike.

Doctor Pike is board certified in medical toxicology and occupational and environmental medicine.[28] Tr. at 5-6; Pet. Ex. 9 at 2. He is currently employed as an emergency room physician and toxicologist. Tr. at 5. He is also the sole professional employee of a corporation, EnviroMD, Inc., that he formed in 1986, through which he does consulting work. Tr. at 36-37; Pet. Ex. 9 at 8-10. Although the corporation was once much larger and performed a variety of environmental work, it currently is the vehicle through which he tracks his time and performs billing. The corporation no longer has separate office space; Dr. Pike does corporation work at the emergency department or in the special procedures area of the hospital where he is employed. Tr. at 36-37. He deals with some neurological events such as stroke in the emergency department where he works (Tr. at 34), but there was no testimony or other evidence indicating that he treats or diagnoses GBS.

Doctor Pike devotes slightly less than 20% of his time to medical-legal work, and derives a similar percentage of his income from such work. Tr. at 38. He has twice testified for petitioners in Vaccine Act hearings, and has written opinions in four to six cases. Tr. at 38-39.

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[28] He also holds J.D. and M.B.A. degrees. Tr. at 5, 39; Pet. Ex. 9 at 2. Petitioner's Exhibit 9, Dr. Pike's curriculum vitae, and Pet. Ex. 10, Dr. Pike's initial report, both contain page numbers in addition to the computer generated exhibit labels. In this decision, I will refer to the computer generated labels in the lower right corner of each page, rather than the pagination in the original documents.

He has authored no peer reviewed publications on GBS, vaccines, or vaccine reactions. Tr. at 40; Pet. Ex. 9 at 13-15 (listing publications). However, he performs risk assessments in his role as an environmental toxicologist and considers vaccines to fall within his toxicological specialty because a vaccine "is essentially a foreign material that is injected into a person's body," which induces a reaction. Tr. at 7.

2. Doctor Feinberg.

Doctor Feinberg is an adult neurologist, who is board certified in neurology and electrodiagnostic medicine. Tr. at 88; Res. Ex. C at 3. After his residency training, he completed a fellowship in neuromuscular disease and clinical neurophysiology at Harvard Medical School. Tr. at 87; Res. Ex. C at 1.

He is currently the chief medical officer of Pennsylvania Hospital, which is part of the University of Pennsylvania health system. He also holds a full-time faculty appointment as an associate professor of clinical neurology at the University of Pennsylvania. Tr. at 88.

Doctor Feinberg spends about 30% of his time in clinical medicine, with the remainder devoted to teaching medical students and neurology residents and administrative duties associated with his chief medical officer role. Tr. at 89. He was the patient safety officer for Pennsylvania Hospital for about 10 years, during which his clinical medical duties were more substantial. *Id.*; Res. Ex. C at 3.

He has consulted on about six vaccine injury cases, but this was his first hearing in the Program. He participates in approximately ten cases per year outside the Program, with one or two typically involving testimony, but less than 5% of his time (and the same percentage of his income) is devoted to medical-legal work. Tr. at 90-91. As an expert outside the program, he has been involved with malpractice, personal injury, and patient safety and risk management cases, and has testified for both plaintiffs and defendants in such litigation. Tr. at 121-22.

He has diagnosed between five and seven patients a year with GBS over the last 15 years. Additionally, he has cared for hundreds of patients diagnosed by others in the medical group in which he practices and during his years as a resident and fellow. Tr. at 89-90. He teaches medical students and residents about GBS as a part of his teaching duties. Tr. at 89, 99-100. He has written about peripheral neuropathies.[29] Res. Ex. C at 10-12 (listing publications).

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[29] GBS is classified as a peripheral neuropathy. *See* Part IV.B., below.

B. Guillain-Barré Syndrome.

Given that there was no contest concerning William's diagnosis, there was little testimony about GBS itself. However, several of the medical journal articles and other evidence filed, including Dr. Pike's initial report (Pet. Ex. 10), discussed the diagnostic criteria, typical clinical presentation, and probable causes. A brief explanation of the syndrome will aid in understanding the causation theories presented.

GBS is a peripheral neuropathy "characterized by various degrees of weakness, sensory abnormalities, and autonomic dysfunction." Haber (2009), Pet. Ex. 36, at 310.[30] The flaccid weakness or paralysis is bilateral and usually symmetric. *See* Pet. Ex. 25.[31] Deep tendon reflexes are reduced or absent in the affected limbs. *Id.*; D. McGillicuddy, et al., *Guillain-Barré Syndrome in the Emergency Department*, ANNALS EMERG. MED., 47(4): 390-93 (2006), filed as Pet. Ex. 22, at 390. GBS is a monophasic illness, with the nadir of symptoms occurring between 12 hours and 28 days after onset. Pet. Ex. 25. Electromyelograph results and analysis of cerebrospinal fluid are confirmatory for diagnosis, but diagnosis can been made in their absence. *Id*.

William's presentation was relatively typical, with onset marked by numbness and tingling in his extremities on or about August 26, 2008, followed by progressive weakness peaking at the time of or shortly after his hospital admission on August 28, 2008. Tr. at 92; Pet. Ex. 3, pp. 87-91, 122-24. William's significant degree of recovery is also fairly typical, although GBS can be fatal. *See, e.g.*, 1994 IOM Report, Pet. Ex. 26, at 38 (noting that GBS has a 5% mortality rate, with 15-20% of survivors experiencing some residual problems, and about 5% having serious residual difficulties).

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[30] This article was based on a review of all peer reviewed medical literature pertaining to vaccines and GBS published between 1950 and 2008. The authors also examined VAERS data for reports of GBS following vaccination, and compared reports to the background rate of GBS.

[31] This exhibit is a one page document constituting the Brighton Collaboration Case Definition for Guillain-Barré syndrome, published by the Centers for Disease Control and Prevention ["CDC"]. The Brighton Collaboration is an international group of vaccine safety experts. One of the Collaboration's roles is establishing standard case definitions for various illnesses and disorders that are temporally related to vaccinations, known as "adverse events following immunization." *See* https://brightoncollaboration.org/public/what-we-do.html (last viewed June 21, 2013). Standardized case definitions improve the quality of research, allowing comparisons among researchers and in surveillance systems and clinical trials. Pet. Ex. 25; Varricchio, Res. Ex. J, at 289 (noting Brighton definitions for vaccine adverse events should result "not only in higher quality reports but also in more rigorous analysis of VAERS data"); *see also Henderson v. Sec'y, HHS*, No. 09-616V, 2012 WL 5194060, at *10 n.45 (Fed. Cl. Spec. Mstr. Sept. 28, 2012). The case definitions appearing in Pet. Ex. 25 are based on three medical journal articles that were also filed as exhibits (Pet. Exs. 15, 16, and 24).

GBS "is mediated by an immune response that results in the direct destruction of either the myelin sheath surrounding the peripheral nerves or the axon itself." T. Lasky, et al., *The Guillain-Barré Syndrome and the 1992-1993 and 1993-1994 Influenza Vaccines*, NEW ENG. J. MED., 339(25): 1797-1802 (1998) ["Lasky"], filed as Pet. Ex. 21, at 1797; Tr. at 100-01. When only the myelin sheath is damaged, GBS is often referred to as AIDP. When the axons are damaged (the axonal variant or acute motor axonal neuropathy ["AMAN"]), the prognosis is worse.[32]

The precise biological mechanism responsible for the immune mediated attack is unclear. GBS has been long associated with upper respiratory infections (which are largely viral in nature)[33] and with gastrointestinal illnesses, particularly diarrheal illnesses, and, more specifically, those caused by the bacterium *Campylobacter jejuni* ["*C. jejuni*"]. *See* Rees, Res. Ex. F, at abstract (noting that approximately two-thirds of GBS patients have an infection preceding their GBS diagnosis, usually involving a mild respiratory or gastrointestinal illness); 1994 IOM Report, Pet. Ex. 26, at 39 (over half of all GBS patients "have a history of a preceding acute infectious illness, either respiratory or gastrointestinal, in the 1 to 4 weeks prior to the onset of neuropathic symptoms"). GBS has also been noted to occur after surgery, in Hodgkin's disease and other lymphomas, and after some vaccinations, including swine flu and rabies vaccines created using neuronal tissue. 1994 IOM Report, Pet. Ex. 26, at 39. However, "with rare exceptions, associations between vaccines and GBS have been only temporal.

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[32] This variant, which accounts for about 20% of GBS cases in the United States, is more frequently associated with preceding *Campylobacter jejuni* ["*C. jejuni*"] infections. *See* J. Rees, et al., *Campylobacter Jejuni Infection and Guillain-Barré Syndrome*, NEW ENGL. J. MED., 333(21): 1374-79 (1995) ["Rees"], filed as Res. Ex. F. In this prospective case control study, 26% of patients with GBS had evidence of *C. jejuni* infection, as compared to 1% of age-matched hospital controls, and those with confirmed *C. jejuni* infections were more likely to have a poor outcome and axonal damage. *See also* Tr. at 112-13.

[33] In testimony, Dr. Pike disagreed that upper respiratory infections are a commonly reported antecedent event (Tr. at 51), contradicting his own report (Pet. Ex. 10 at 13), in which he stated that they were a trigger for GBS. Whether respiratory infections are responsible for most GBS cases is hard to determine, but they certainly play a significant role in causing or triggering many cases of GBS. The relationship between viral infections, and in particular, upper respiratory infections, is well supported, not only by the testimony of Dr. Feinberg, but also by the medical literature cited by Dr. Pike in his reports. *See, e.g.*, 1994 IOM Report, Pet. Ex. 26, at 39; V. Sivadon-Tardy, et al., *Guillain-Barré Syndrome and Influenza Virus Infection*, CLIN. INFECTIOUS. DIS., 48(1): 48-56 (2009) ["Sivadon-Tardy"], filed as Pet. Ex. 45 and Res. Ex. G, at 48 ("GBS occurs after acute infectious disease (usually respiratory tract infections . . . or gastrointestinal illness) . . . in 60%-70% of patients"); J. Stübgen, *Neuromuscular complications of hepatitis A virus infection and vaccines*, J. NEUROL. SCI., 300: 2-8 (2011), filed as Pet. Ex. 47, at 3 ("Guillain-Barré syndrome (GBS) is commonly triggered by viral infections"). I also note that Dr. Pike relied on reports that viral illnesses may cause GBS for his opinion that some of the vaccines William received could do so.

There is little evidence to support a causal association with most vaccines." Haber (2009), Pet. Ex. 36, at abstract and 310.

How these diverse events cause or trigger the immune system to target host tissue, the myelin "insulation" around peripheral nerves or the axons themselves, is not known.[34] As both expert witnesses testified, the most commonly postulated mechanism involves "molecular mimicry." Tr. at 11-13, 83, 100-01; *see also* Haber (2009), Pet. Ex. 36, at 312 (describing molecular mimicry as occurring when the epitopes of a vaccine initiate the development of antibodies and/or T cells that could cross-react with epitopes on myelin or the glycoprotein of axons of peripheral nerves). Alternatively, destruction of axonal or myelin membranes could be caused by "vaccine virus or vaccine-associated products." Haber (2009), Pet. Ex. 36, at 312. Damage to supporting cells could involve the insertion of virus associated peptides into cells, triggering an immune attack on those cells. Another possible mechanism would involve the activation of antibodies against myelin that are already present in the body. *Id*.; Tr. at 13; Pet. Ex. 14 at 6-8.

Causal relationships between potential inciting events and GBS have proven difficult to demonstrate, because of the absence of specific biological markers. Haber (2009), Pet. Ex. 36, at 312 (noting that "the association of a prior infection or vaccination with development of GBS is based upon a close temporal relationship and additional supportive epidemiological evidence"). The authors of this review article noted that the evidence is "particularly strong" for *C. jejuni*, cytomegalovirus, and *M. pneumoniae* infections, but not definitively substantiated. The association with vaccines is strongest for the 1976 swine flu vaccine, and for rabies vaccines produced using brain tissue. *Id*. Likewise, no biological mechanism for the demyelination has been identified, even for these vaccines recognized as causally linked to GBS. *Id.*

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[34] *See* Haber (2009), Pet. Ex. 36, at abstract ("Although the underlying aetiology and pathophysiology of GBS are not completely understood, it is broadly believed that immune stimulation plays a role in its pathogenesis."); *see also* A. Ropper & M. Samuels, ADAMS AND VICTOR'S PRINCIPLES OF NEUROLOGY, McGraw-Hill Companies (9th ed. 2009) [Ropper & Samuels, NEUROLOGY] at 1266 ("An unanswered question is what incites the immune reaction isolated to peripheral nerves in humans. All attempts to identify a virus or microbial agent within nerves have failed . . . .").

C. Evaluating Petitioner's Evidence.[35]

1. Treating Doctors.

No treating doctor opined that William's GBS was causally associated with his vaccinations. At best, some treating physicians noted that he had received vaccinations in the month or six weeks prior to onset of symptoms, but they also noted the upper respiratory infection two weeks prior to onset. *See, e.g.*, Pet. Ex. 2, p. 2.

Petitioner relied on statements by Dr. Lopez, who apparently worked at an Air Force vaccine safety office, regarding possible vaccine causation. Doctor Pike intimated that this record was that of a treating physician, but it is clear that this record (Pet. Ex. 3, p. 3) involved a telephone consultation in an effort to track down information connected to a VAERS report regarding William's GBS. Doctor Pike failed to note that, based on this record, Dr. Lopez was stationed at Lackland Air Force Base, located in San Antonio, TX, while William attended boot camp and received his medical treatment at military installations in California and was still in California on the date reflected on this record. Thus, it is unlikely that Dr. Lopez was a "treating physician."

Furthermore, Dr. Pike took statements from Dr. Lopez regarding causation out of context. *See* Pet. Ex. 10 at 10 (section titled "Vaccine Healthcare Center Recognized Vaccine Caused GBS"). Doctor Lopez noted that post-marketing surveillance reports appearing on the package inserts from several of the vaccines William received listed GBS as an adverse event occurring post-vaccination. As Dr. Pike acknowledged during his testimony, reports of GBS (and many other conditions) appear in package inserts without any attribution of causality. Tr. at 72-74. They may merely reflect a temporal relationship between vaccine and illness.[36] In this regard, they are on par with VAERS reports, which are not probative evidence of vaccine causation. *Supra* at n.25.

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[35] Although I have read and considered all of the medical literature filed by the parties in this case, some of the medical literature referenced in Dr. Pike's reports and filed as petitioner's exhibits is not summarized in this discussion. In view of Dr. Feinberg's acknowledgment that GBS is an immune mediated condition and that stimulation of the immune system by infections appears to trigger its development, the references such as Pet. Exs. 41 and 43 pertaining to autoimmunity appear superfluous. As William did not receive an influenza vaccine, articles discussing the relationship between influenza vaccines and GBS are only tangentially relevant (*e.g.*, Pet. Exs. 23, 24), and most are not discussed at length. Finally, as Dr. Pike testified that he thinks there is insufficient evidence that the hepatitis B vaccine played a role in William's development of GBS, the references to that vaccine, which include Pet. Exs. 38, 42, and 48, are not discussed. *See* Tr. at 10, 83-84. The failure to discuss any of the exhibits filed should not be viewed as an indication that I did not consider them.

[36] *See Werderitsh v. Sec'y, HHS,* No. 99-319V, 2005 WL 3320041, at *8 (Fed. Cl. Spec. Mstr. Nov. 10, 2005) (quoting 21 C.F.R. § 600.80(l) as saying "[a] report or information submitted by a licensed manufacturer . . . does not necessarily reflect a conclusion by the licensed manufacturer or FDA that the

The only reference in Dr. Lopez's record that cites a causal relationship between a vaccine and GBS is based on the 1994 IOM Report. The 1994 IOM Report found mechanistic evidence that causally linked tetanus vaccination to GBS. This report is discussed in more detail below, but in summary, the 1994 IOM Report's conclusions in this regard were changed in the most recent IOM report ["2011 IOM Report"], filed as Res. Exs. A and I.[37]

2. Summary of Dr. Pike's Reports and Testimony.

Doctor Pike's reports and testimony presented something of a moving target regarding the theories of vaccine causation on which he relied. The most consistent part of Dr. Pike's opinions is that both sets of vaccinations, plus the synergistic effects of administering the second set while William was in the "acute phase" of an upper respiratory infection, caused William's GBS. Pet. Exs. 10 at 7, 21; 14 at 1; Tr. at 18-19, 44.

To the extent that Dr. Pike discussed theories of causation in his initial report, the focus was on the synergistic impact of two sets of multiple vaccinations, combined with vaccinations received during "active infection." Pet. Ex. 10 at 21. He testified that he did not provide supporting literature citations for this assertion because it was based on his own experience. Tr. at 41-42. His theories for how multiple vaccines, plus an intercurrent infection, could result in GBS were not well articulated, appeared contradictory with other theories he presented, and totally lacked scientific support.

His second report briefly discussed many theories about how autoimmune diseases are caused, but Dr. Pike did not appear to endorse any specific theory. Although he devoted the most time and attention to a molecular mimicry theory in this report, he also postulated that the egg protein in which some vaccines are grown, adjuvants in vaccines, vaccines themselves, and the pertussis toxin in particular could all induce an aberrant immune response. *See generally*, Pet. Ex. 14 at 3-10. Additionally he asserted that some of the diseases against which William was

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report or information constitutes an admission that the biological product caused or contributed to an adverse effect"); *see also Christiansen v. Sec'y, HHS*, 08-244V, 2012 WL 6766650 (Fed. Cl. Spec. Mstr. Nov. 13, 2012).

[37] In his second report, Dr. Pike referred to Res. Ex. A as "unpublished," implying that the 2011 IOM Report was therefore unreliable as evidence. While it is true that unpublished reports and studies are generally accorded little or no weight, the "unpublished" version of the 2011 IOM Report was a pre-publication, uncorrected proof copy of the report, made publically available in electronic form prior to the release of the final printed publication. Respondent's Exhibit I includes excerpts from the published version of the report. All citations to the 2011 IOM Report in this decision will use the page numbers of the published version, filed as Res. Ex. I.

vaccinated were causally associated with GBS and reasoned that the vaccines therefore could cause GBS as well.

At various points in each of his two expert reports, Dr. Pike also identified specific vaccines as likely to be causal. The lists of likely causal vaccines included the two vaccines that do not appear on the Vaccine Injury Table. However, the order in which he singled out specific vaccines as likely culprits varied from report to report, and even within reports.[38]

At the hearing, Dr. Pike again claimed that all of the vaccines, plus the upper respiratory infection, caused William's GBS. Tr. at 9-10, 17-19. Although he maintained this position, he devoted a considerable portion of his testimony to two specific vaccines, the tetanus component of the Tdap vaccine and the yellow fever vaccine received on August 22. He also specifically commented on the causal role played by the MMR vaccine received on July 23, 2008.

The issue of appropriate timing was also a thread that ran through Dr. Pike's reports and which formed part of the basis for his causation theories.

3. A Reliable Medical Theory: Althen's First Prong.

This section discusses the evolution of Dr. Pike's theories and the evidence regarding specific vaccines. His initial report, discussed in subsection a, contained most of the VAERS data upon which he relied. Most of the theories were presented in his second report, which are discussed in subsection b. The evidence for a causal role for individual vaccines appears in subsection c. Subsection d contains a summary and my conclusions.

a. The Initial Report and VAERS Data.

In the analysis section of his initial report (Pet. Ex. 10 at 20-21), Dr. Pike stated:

> When any vaccine is administered in the presence of an infection the risk of acquiring *Guillain-Barré Syndrome* is much greater because of an

[38] The initial report pointed to the MMR, pneumococcal, hepatitis A and B (Twinrix), and meningococcal vaccines as those "most likely impacted" in the development of William's GBS, and the Tdap, second Twinrix, polio, varicella, and yellow fever vaccines as being "implicated independently as substantial causal factors." Pet. Ex. 10 at 7-8. However, in the conclusion section of the report, Tdap was included in both categories; those vaccines "most likely impacted" and those "implicated independently." *Id.* at 23. In his supplemental report, Dr. Pike singled out Tdap, hepatitis A and B, MMR, pneumococcal, and meningococcal vaccines as those "most likely causally implicated." Pet. Ex. 14 at 1-3.

> active systemic inflammatory response that is present. The risk is independently and substantially magnified when multiple vaccines are given simultaneously. When multiple vaccines are administered to an individual suffering from an upper respiratory infection that risk is unacceptably high.

Id. at 21. There were no citations to any authority for these statements, which are the closest thing to a theory of causation present in the initial report. He appeared to presume, based on his VAERS research (which is discussed at pages 14-17 of Pet. Ex. 10), that the issue of vaccine causation of GBS was well-established simply by the existence of VAERS reports. However, with the exception of the influenza vaccine, none of the medical journal articles he cited support vaccine causation of GBS, and none support causation at all by any of the vaccines William actually received.

His conclusions must therefore be supported, if at all, by his own VAERS research. There were two areas of focus to this VAERS research: (1) the time periods between vaccination and reports of onset of symptoms of GBS, and (2) the relative percentages of reports of GBS following specific vaccinations. The problems in relying on Dr. Pike's research to establish that the vaccines William received, alone or together, can cause GBS are numerous.

Reproducibility is the hallmark of good science.[39] Doctor Pike was not precise about how he arrived at the results reflected on the charts in his report, thus it would be impossible to duplicate his results. From the results he obtained, it appears that he examined all cases of GBS in the VAERS database. Each chart represents a different analysis of a subset of that data.

However, the uncertainty in his methodology, as important as that is in assessing reliability, is not the most significant problem in evaluating Dr. Pike's results. The more fundamental problem is that Dr. Pike was fishing for data in a stocked pond, and then extrapolating from the resulting catch to opine on the fish population of a nearby lake. VAERS is a stocked pond. It only contains reports (many of which are unverified or incomplete)[40] of adverse events after vaccinations. VAERS contains no reports or data about the relative rate of these same events in individuals who have not been vaccinated. Thus, the number of specific adverse events, such as GBS, reported after

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[39] *See Daubert*, 509 U.S. at 593-94.

[40] For example, Dr. Pike's own research revealed that over 9% of the cases of GBS reported after influenza vaccine did not include a date for onset of symptoms. *See* Pet. Ex. 10 at 14 (chart and explanation for the data presented).

any vaccine, is meaningless without information about the background rate of that adverse event and information about the number of vaccines administered.[41]

Leaving these fundamental problems aside, I have specific problems with how Dr. Pike presented the data he found and the conclusions he drew from this data. These problems with Dr. Pike's research are addressed below.

(1) Timing.

Timing of an adverse event after vaccination can be significant for a conclusion regarding causality. For example, one of the many reasons for concluding that there was a causal connection between the mass swine flu vaccination program of 1976-77 and increased reports of GBS was a clustering of GBS cases in the second and third weeks after vaccination. Langmuir, et al., *An Epidemiologic and Clinical Evaluation of Guillain-Barré Syndrome Reported in Association With the Administration of Swine Influenza Vaccines,* AM. JOURNAL OF EPIDEMIOLOGY, 119(6): 841-79 (1984), filed as Pet. Ex. 20, at 860-63; Haber (2004), Pet. Ex. 17, at 2478. However, in the absence of clustering, the fact that cases of GBS are reported after vaccination says little to nothing about a causal connection between GBS and vaccination, other than causation is possible.[42] If the theory of causation has temporal limits—a window of time based on the biologic processes involved—in which causation can occur, these windows can be used to differentiate which cases may be causally connected from those in which a causal connection is unlikely.

The narrative portion of Dr. Pike's initial report discussed several epidemiologic studies of GBS and the mass swine flu immunization program in 1976-77, focusing on the timing of onset of GBS after vaccine administration. Pet. Ex. 10 at 12-13. He noted that reports of GBS began in the first week after vaccination, and peaked in the second and third weeks, with the highest incidence occurring 17 days after swine flu vaccination.[43] Pet. Ex. 10 at 12-13.

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[41] This was the approach taken in the Haber 2009 article, Pet. Ex. 36. The authors looked at GBS reports in VAERS after various vaccines, and compared the reports to the background rates of GBS in the general population. Pet. Ex. 36 at 313-18.

[42] Our caselaw acknowledges the scientific principle that a temporal connection, standing alone, is insufficient to establish vaccine causation. *Strother v. Sec'y, HHS,* 18 Cl. Ct. 816 (1989), *aff.*, 950 F.2d 731 (Fed. Cir. 1991); *see also Grant v. Sec'y, HHS,* 956 F.2d 1144, 1148 (Fed. Cir. 1992) (a vaccination is not the cause for all events that follow it); *Cedillo v. Sec'y, HHS,* 89 Fed. Cl. 158, 176 (Fed. Cl. 2009), *aff.,* 617 F.3d 1328 (Fed. Cir. 2010) (affirming the special master's rejection of the petitioners' vaccine causation argument because the treating doctors were recognizing a mere temporal relationship).

[43] With regard to other influenza vaccines, Dr. Pike cited to the Lasky article, Pet. Ex. 21, to show that the peak onset interval between vaccine and GBS was between nine and 12 days after vaccination, with

Thereafter, Dr. Pike used his own research into timing between vaccination and onset of GBS as reported in VAERS to draw conclusions about vaccine causation. There are two major problems with this timing research. The first is the unstated assumption that VAERS reports of GBS after vaccination represent actual vaccine causation of GBS, rather than simply cases temporally associated with vaccines.[44]

The second problem is the skewed way he displayed the data. Doctor Pike used VAERS reports of GBS to establish that vaccines could cause GBS as early as the date of administration and as late as 120 days after administration, although he settled on a peak period of risk of 10-60 days. Pet. Ex. 10 at 15. The fallacy in this approach is obvious, as Dr. Pike must presume that VAERS reports represent the actual incidence of vaccine-caused GBS in order to use the timing of these reports to demonstrate a medically appropriate temporal relationship. His logic is circular, using a report from VAERS of GBS onset on Day 1 (the day after vaccine administration) and on Day 60 to prove that vaccines can cause GBS as early as Day 1 or as late as Day 60. However, there is no proof that the vaccine was responsible for the GBS reported in either case, let alone whether the reported diagnosis was correct or that a vaccine was actually received. *See generally*, Varricchio, Res. Ex. J.

He attempted to skirt this issue by first examining VAERS reports of GBS following influenza vaccines to try to define appropriate temporal relationships, apparently assuming that all VAERS reports of GBS following influenza vaccine would represent actual vaccine-caused GBS. The evidence for this point is lacking. Examining Dr. Pike's own references, I note that even when there is evidence that influenza vaccines (other than the swine flu vaccine administered in 1976-77) can cause GBS, the number of excess cases of GBS caused is quite small, on the order of 1-2 extra cases of GBS per million doses of influenza vaccine. Lasky, Pet. Ex. 21, at 1801. The vast majority of cases of GBS are attributed to other causes, such as upper respiratory or gastrointestinal infections or unknown causes. 1994 IOM Report, Pet. Ex.

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some cases reported within seven days of vaccination. Pet. Ex. 10 at 12-13. He acknowledged that "some investigators" did not include the first seven days after vaccination in the risk period, citing to D. Juurlink, et al., *Guillain-Barré Syndrome After Influenza Vaccination in Adults,* ARCH. INTERN. MED. 166: 2217-21 (2006) ["Juurlink"], filed as Pet. Ex. 18, as an example. There are some areas of concern in Dr. Pike's discussion of these papers. For example, he referred to the epidemiological studies on page 12 of his report as "controlled" when they were not controlled studies and he concluded, without any support, that GBS occurring in the first seven days after vaccination is the result of "individual variability in susceptibility to illness and immune response." Pet. Ex. 10 at 12.

[44] Other presumptions are necessary as well, including that the vaccine listed was actually administered, the diagnosis of GBS is correct, and no other known causes for GBS occurred in the appropriate time period prior to onset.

26, at 39. Thus, even with regard to reports of GBS following influenza vaccine in VAERS, causation cannot be presumed. Varricchio, Res. Ex. J, at 289-90.

Doctor Pike tried to use spikes in the VAERS data as evidence of vaccine causation.[45] That is, following the approach taken in examining the swine flu vaccine cases, if reports of post-influenza vaccine GBS occur in groups at specific time periods after vaccination, they may constitute evidence of causation. If similar spikes appear in specific time intervals after the vaccines that William actually received, the similarity might serve as evidence of causation by those vaccines. The approach itself has some merit, but the execution was flawed in this case. Doctor Pike generated the spikes artificially by the skewed way he grouped the reports.

The charts Dr. Pike prepared from his data appear in Pet. Ex. 10 at 14 (influenza data)[46] and 16 (data from vaccines administered to William).[47] In both charts,[48] spikes in the number of cases appear at Days 10-14, 15-30, and 31-60, as compared to individual days (Days 1, 2, 3, 4, 5, 6, 7, 8, and 9), and grouped days (Days 61-120, over 120, and "unknown.").[49] One need not be a statistician or epidemiologist in order to

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[45] Spikes or clusters of cases occurring at points in time after a potentially causal event are often used by epidemiologists as some evidence that the event in question is causal. For example, in the Lasky paper, Pet. Ex. 21, at 1799 and fig. 2, the distribution of cases of GBS reported after influenza vaccination showed a spike of such cases within the second week after vaccination. When analyzed for statistical significance, the probability of this distribution pattern occurring by chance alone was quite low, and the authors used this spike as some evidence of vaccine causation. *Id*. at 1801. When such clusters occur within an interval appropriate to the biological mechanism suspected, their evidentiary value for causation is enhanced. However, VAERS evidence that an adverse event happened at a particular time after vaccination does not mean that the timeframe between vaccination and event is medically appropriate. Reports of adverse events following vaccines in passive surveillance systems such as VAERS are more likely for events occurring close in time to the vaccination. Haber (2004), Pet. Ex. 17, at 2480; *see also* H. Retaillau, et al., *Illness after Influenza Vaccination Reported Through a Nationwide Surveillance System 1976-1977*, AM. J. EPIDEMIOL., 111(3): 270-78 (1980), filed as Pet. Ex. 23, at 272, 275 (finding interval between vaccination and onset of symptoms in passive reporting system was generally less than two days and noting that GBS was the only disease more commonly reported in the second and third week after vaccination).

[46] According to Dr. Pike, this chart, titled "Onset Interval and Symptoms," represents all the "post-influenza vaccination adverse events recorded in the VAERS database" as GBS.

[47] This chart, titled "Eight Vaccine Onset Interval for GBS After Injection," represents the combined onset intervals for the vaccines William received.

[48] The appendix contains copies of both of these charts.

[49] The high percentage of "unknown" dates of onset (9.3%) itself casts doubt on the reliability of performing research in VAERS to look for trends in onset intervals to demonstrate vaccine causation.

observe that the spikes in both charts are produced by the way the reports are grouped, comparing aggregated data for intervals of five, 16, and 30 days to data from individual days, to produce these spikes.[50]

Doctor Pike asserts that the influenza vaccine data establishes the following facts: (1) most cases of GBS after influenza vaccinations occurred in a two to twelve week window; (2) peak onset occurred "between 10 and 30 days"; and (3) "a substantial proportion (>26%) also occurred in the first week" after vaccination. Pet. Ex. 10 at 14. He also asserts that the data for the eight vaccines William received demonstrate that most cases of GBS were reported between 10 and 60 days after vaccination. *Id.* at 15.

Doctor Pike relies on this data for the conclusion appearing in Section III of his initial report ("Opinion & Conclusions"), which states: "The likelihood of developing post-vaccination Guillain-Barré Syndrome all within thirty to sixty days post-vaccination from any other cause but for the July 23, 2008 and August 22, 2008 vaccination[s] is extremely rare."[51] Pet. Ex. 10 at 8. The only possible basis for this statement found in his report is the VAERS data that showed onset intervals for GBS "most often reported

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[50] This can be illustrated thusly from the influenza chart, Pet. Ex. 10 at 14, which shows that 20% of cases occurred on Days 10-14, a five-day period. Thus, on average, 4% of the cases occurred on any one day during the spike found at Days 10-14. The spike disappears when this average is compared to the percentages reported for individual days on Days 0-9 (*e.g.*, Day 0 had 4.3% of the cases; Day 1 had 4.9% of the cases, Day 7 had 3.7% of the cases, and Day 9 had 4.6% of the cases). When the data are examined day by day as a percentage of the total cases reported, there are no spikes or clusters. To compare the data another way, if the cases occurring in the first 15 days after vaccination are grouped into equal intervals of five days each (Days 0-4, Days 5-9, and Days 10-14), the percentages of cases reported as occurring within those intervals are quite similar (17.6% occurring on days 0-4, 16.8% on days 5-9, and 20% on days 10-14). There may still be a small spike on days 10-14, but whether it is statistically significant (or says anything at all about the possibility of vaccine causation) is unknown. What is glaringly obvious is that Dr. Pike grouped the data the way he did so as to make a large spike in cases <u>appear</u> to occur at days 10-30.

Similar data manipulation appears on the "Eight Vaccines" chart, which records onset intervals reported for the vaccines that William actually received, but this chart lacks the percentage labels for the bars on the graph. The two large spikes similarly appear at Days 10-14 (about 19% of cases) and Days 15-30 (about 22% of cases), with a smaller spike at Days 31-60 (about 12% of cases) and, when aggregated, they account for about 53% of the cases reported post vaccination. However, when the percentages reported are grouped in similar intervals of five days each, the spike at 10-14 days disappears, as it is roughly equal to the Day 0-4 and Day 5-9 groups. There is no spike on Days 15-30 when the 22% is divided among 16 days in this grouping.

[51] As written, this statement could be considered a tautology rather than a conclusion. By its very terms, "post-vaccination Guillain-Barré syndrome" only occurs post vaccination. I presume that what Dr. Pike meant to say is that it would be extremely rare for something, other than a vaccination, to cause any case of GBS occurring within 30-60 days after a vaccination. That conclusion is still suspect, but it is a conclusion rather than a tautology.

between 10 and 60 days" post vaccination for the group of vaccines William actually received. Pet. Ex. 10 at 15.

To draw such a causality conclusion from the timing data requires one to presume that all cases of GBS reported in VAERS post-vaccination are indeed vaccine caused. Furthermore, if Dr. Pike's statement is correct (and it can be correct only insofar as vaccine adverse events involving GBS reported to VAERS are concerned), William's second set of vaccinations occurred too soon (four days prior to onset of symptoms) to be in the 30-60 day window, and for the 10-30 day window, neither set of vaccines was administered in the period of peak risk he found.[52]

(2) Relative Risk as a Percentage of Cases.

Doctor Pike also compared the relative frequency in VAERS of GBS reports following the vaccines William actually received. Pet. Ex. 10 at 16. The chart he developed indicates via bar graphs that MMR, pneumococcal, and Tdap vaccines accounted for the most reports of post-vaccine (other than influenza vaccine) GBS in VAERS. *Id.* at 17. From this data, Dr. Pike claims, for these eight vaccines, that MMR and pneumococcal vaccines account for over 50% of the GBS vaccines cases in VAERS. He also computed the percentages for hepatitis A and B (about 10%), meningococcal (about 6%), Tdap (17%), polio (8%), and varicella (6%). I note that the two vaccines that do not appear on the Vaccine Injury Table, yellow fever and the adult pneumococcal vaccines, account for 37% of the cases of GBS reported after the vaccines William received.

What Dr. Pike did not tell us, at least in his initial report, is how many reports were involved and how many doses of each of these vaccines were administered. Comparing, as Dr. Pike did, the number of adverse events after one vaccine to the number after another vaccine is useless unless one knows how many vaccines of each type were administered.[53]

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[52] The July 23 vaccinations were administered 34 days before onset of GBS symptoms; and the August 22 vaccinations were administered four days prior to onset. Other evidence also indicates that the August vaccinations were received too close in time to be causal. 1994 IOM Report, Pet. Ex. 26, at 45. Additionally, Dr. Pike relied solely on VAERS reports following influenza vaccine, a vaccine William did not receive, to conclude onset should occur between 10 and 30 days following vaccination. Pet. Ex. 10 at 12.

[53] For example, influenza vaccines are recommended for annual administration to a substantial percentage of the U.S. population. A tetanus vaccination is recommended for adults in the U.S. every ten years. Yellow fever vaccines are recommended only for those traveling to areas where yellow fever is prevalent. Thus, one would expect more reports of GBS following influenza vaccine than after yellow fever vaccine to occur by chance alone because more influenza vaccines are administered annually than yellow fever vaccines. Examined another way, if the total number of GBS cases after these three

An increase in the raw number of reports to VAERS of injury following a particular vaccine cannot be compared from year to year without knowing how many doses of that vaccine were administered. For example, there were 27 reports to VAERS of GBS following influenza in the 1991-92 flu season; 37 in 1992-93, and 74 in 1993-94. This would suggest that the 1993-94 vaccine was more likely to cause GBS. However, the actual risk was about the same for 1992-93 and 1993-94, because of differences in the number of vaccinations administered. Lasky, Pet. Ex. 21, at 1800; *see also* Varricchio, Res. Ex. J., at 290 (noting that incidence rates cannot be calculated from VAERS reports).

b. Theories.

In his second report and in his testimony, Dr. Pike identified several vaccines as "most likely causally implicated," although he continued to adhere to his position that all the vaccines William received contributed to causing his GBS. Pet. Ex. 14 at 1; Tr. at 83-84. Although he identified a number of theories of causation,[54] he never specified a particular theory as the most likely causal mechanism in William's case. His discussion of causation theories in his second report is rambling and it is not entirely clear to what extent, if any, he relies upon any of the theories set forth. The section of the report dealing with theories appears to contain summaries of several general theories of autoimmunity set forth in the articles cited, without focus on how such theories relate to GBS or the specific vaccines that William received. *See generally*, Pet. Ex. 14 at 3-10. However, the molecular mimicry theory received the most attention, both in testimony and in Dr. Pike's report.

(1) Molecular Mimicry.

Molecular mimicry is the theory of causation most often cited in the medical literature with regard to how GBS is caused. There is some evidence to support vaccine causation of GBS via this mechanism, particularly in the case of rabies vaccines containing brain tissue. 1994 IOM report, Pet. Ex. 26, at 44 (noting that "most

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vaccines is 100, and the number following influenza vaccine is 90, tetanus is 8, and yellow fever is 2, one cannot draw a conclusion about the relative risk of GBS after influenza as being many times higher than the risk after yellow fever without knowing how many influenza vaccines were administered versus yellow fever vaccines. Doctor Pike did this calculation in his second report, but he did not compare the rates of GBS reported after various vaccines to the background rate of GBS in the population.

[54] Doctor Pike listed and briefly discussed molecular mimicry, egg protein, endotoxin, an autoimmune response to viral peptides, release of myelin antigens, adjuvants, and illness, in addition to the general immune activation theory mentioned in his first report, as theories of how GBS is caused. These are the same theories mentioned in the Haber 2009 article, Pet. Ex. 36, and in the 1994 IOM report.

authorities believe that the neuroparalytic events that occur following receipt of [rabies vaccines produced in nervous tissue of an infected animal] are related to an immune response to admixed neural constituents in the inoculum").

When the immune system is confronted with a pathogen (which could be viral or bacterial), the body produces antibodies. According to the molecular mimicry theory, GBS occurs when these antibodies cross react with epitopes on the surface of peripheral nerves and attack either myelin or glycoproteins on the nerve surface. Haber (2009), Pet. Ex. 36, at 312; Pet. Ex. 14 at 4-5. Or, as Dr. Feinberg simply explained the theory, something in the immune system goes awry, and misidentifies some of the body's own cells as those of the invading microorganism. The theory requires that the proteins found in the invading microorganism share some genetic sequences with the specific host cells attacked. Exact homology with the host tissue is not necessary. Tr. at 100-01; *see also* Haber (2009), Pet. Ex. 36, at 312; Pet. Ex. 14 at 5.

In GBS, the theory is specific to the myelin sheaths insulating the axons of the peripheral nerves (or in the case of the axonal variant, the axons themselves) as the subject of this autoimmune attack. Haber (2009), Pet. Ex. 36, at 312.

(2) Egg Protein/Endotoxin Theories.

In testifying about the MMR and yellow fever vaccines, Dr. Pike indicated that an egg-based "P2" protein was associated with GBS, and that both of these vaccines were processed in eggs. Tr. at 15. He testified that the yellow fever vaccine has the highest content of egg protein of a type shown to induce GBS symptoms in animal models. Tr. at 15-16.

Aside from an article[55] authored by Dr. Mark Geier,[56] there was very little other evidence regarding P2 protein and GBS. The Haber 2004 article (Pet. Ex. 17)

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[55] M. Geier, et al., *Influenza vaccination and Guillain Barré syndrome*, CLIN. IMMUNOL.,107: 116-21 (2003) ["Geier"], filed as Pet. Ex. 34, at 120 ("We believe there may be chicken P2 protein present in influenza vaccines (influenza vaccines prepared from the allantoic fluid of chicken embryos), despite some previous studies to the contrary that may have lacked appropriate controls [] and that P2 protein may be the target for a humoral or cell-mediated immune reaction observed in patients developing GBS following influenza vaccination.").

[56] Given what other courts (and the IOM) have concluded about the quality and reliability of Dr. Geier's research, I attach no weight to this article's conclusions about the role of the P2 protein in causation of GBS. *See Graham v. Wyeth Labs.,* 906 F.2d 1399, 1418 (10th Cir.1990) (Dr. Geier's calculation error was of sufficient magnitude so as to warrant a new trial); *Redfoot v. B.F. Ascher & Co.,* No. 05–2045, 2007 WL 1593239, at *11 (N.D.Cal. June 1, 2007) (excluding Dr. Geier as an expert, finding his testimony "not reliable"); *Doe v. Ortho–Clinical Diagnostics, Inc.,* 440 F.Supp.2d 465, 474 (M.D.N.C.2006) (excluding Dr. Geier's testimony as based on "hypothesis and speculation"); *Jones v. Lederle Labs.,* 785

mentioned egg-processed vaccines as possibly carrying an increased risk of GBS, but rather than the P2 protein theory, the article speculated that a reduction in *C. jejuni* infections in chickens (and thus in eggs used to manufacture vaccines) might have led to a decline in GBS cases reported during a particular period of time, implying that *C. jejuni* contamination, not P2 protein, was considered the causal agent in this theory. Pet. Ex. 17 at 2480; *see also* J. Winer, et al., *A prospective study of acute idiopathic neuropathy*, *III. Immunological studies*, J. NEUROL., NEUROSURG., AND PSYCHIAT. 51: 619-25 (1988) ["Winer"], filed as Pet. Ex. 29,[57] at 623-24 (finding no increase in antibody responses to human P2 myelin protein in GBS patients as compared to controls).

In his second report, Dr. Pike discussed the level of endotoxin found in the influenza and tetanus vaccines in the same section of the report that also contained his "P2" protein theory. Pet. Ex. 14 at 7. Once again, this was an assertion that relied upon the Geier article, Pet. Ex. 34. Apparently the chain of reasoning was that a causal relationship between tetanus endotoxin and GBS had been established, via the 1994 IOM report. However, that report did not mention endotoxin as a causal mechanism in GBS. *See* 1994 IOM Report, Pet. Ex. 26, at 88-89. Thus, the basis for Dr. Pike's assertion of a relationship between endotoxin in tetanus vaccine and GBS causation is not clear.[58]

F.Supp. 1123, 1126 (E.D.N.Y. 1992) ("the court was unimpressed with the qualifications, veracity, and bona fides" of Dr. Geier); *Militrano v. Lederle Labs.,* 3 Misc.3d 523, 537–38, 769 N.Y.S.2d 839 (N.Y. Sup. Ct. 2003) (characterizing Dr. Geier's affidavit as "conclusory and scattershot" and "undermined by many of the materials submitted in support of it"); IOM 2004 Report at 55-62 (calling his work uninterpretable and noncontributory). I also note that the Geier article itself is tentative regarding the role of egg or P2 protein in causation (*e.g.*, "We believe," "May be the target," "despite some . . . studies to the contrary . . ."). Geier, Pet. Ex. 34, at 120.

[57] This article does not appear to be the article petitioner intended to file. It is not the article which is listed in the bibliography for Dr. Pike's initial expert report. The reference list identifies the second article in a series of articles written about a prospective case control study of GBS, in which patients presenting with GBS were compared to matched hospital controls; the article filed was the third such article. *Compare* Pet. Ex. 10 at 24 (last reference) *with* Pet. Ex. 29 (the only article by Winer filed in this case). The second article (*A Prospective Study of Acute Idiopathic Neuropathy: II. Antecedent Events*), which was described in the 1994 IOM Report, discusses the role of antecedent events in causation; the article filed as Pet. Ex. 29 compares serum from the two groups to measure immune responses.

[58] Doctor Pike opined that "[e]ndotoxin present in vaccines increases antibody production to unrelated antigens and increases the permeability of the blood-brain barrier that can allow proteins having deleterious neurogenic properties to enter the nervous system." Pet. Ex. 14 at 7. Without support, he went on to say that this process "contributes to vaccine-induced autoimmunity and GBS following influenza vaccination." *Id*. I note that except for the Geier article (Pet. Ex. 34), none of the medical literature filed mentions endotoxin as a possible, much less probable, mechanism by which the influenza vaccine causes GBS.

(3) Other Theories.

In one line, without any supporting citations, Dr. Pike asserted that "[d]irect insertion of viral peptides or products into myelin or axonal cell membranes can result in a direct cell-mediated or humoral (antibody) autoimmune response targeted against the affected cell." Pet. Ex. 14 at 6. He also noted that many viral peptides bind to the same sites of antigens as do myelin basic protein. He did not cite to specific evidence suggesting that this process is at work in GBS, although a few of the articles petitioner filed mention this theory as a possibility. *See, e.g.*, Haber (2009), Pet. Ex. 36, at 312; 1994 IOM Report, Pet. Ex. 26, at 46. None indicate that this theory is probable or reliable.

Similarly without citation, Dr. Pike asserted that autoimmune reactions could result from vaccines somehow orchestrating antigens against myelin basic protein already in the body to be released to attack the myelin sheaths or nerve axons. Pet. Ex. 14 at 6-7; Tr. at 14, 16-17. He was not specific about how vaccines could orchestrate the release of such antibodies into general circulation.

In his second report, Dr. Pike also asserted that adjuvants in vaccines could play a causal role in vaccine-induced GBS, because adjuvants are designed "to enhance and accelerate an exaggerated and potent immune response." Pet. Ex. 14 at 9; *see also* Tr. at 14-15. Once again, he offered no support for this theory as a causal mechanism in GBS.

(4) Analysis of Theories in Second Report.

Theories about how vaccines or infections cause GBS abound, but there is little hard evidence to support any of them. This lack of evidence is not fatal to a causation determination, as proof of causation in the Vaccine Program does not require "complete and direct proof of how vaccines affect the human body." *Althen*, 418 F.3d at 1280. The molecular mimicry theory is the one most widely accepted for the agents most frequently accepted as causal. Although there is little evidence to establish homology between something in the influenza virus and the myelin sheath of the peripheral nerves, influenza is widely recognized as a cause of GBS. Likewise, even in the absence of any evidence of homology, at least some versions of the influenza vaccine are thought to cause GBS. Because both wild-type influenza and some specific types of influenza vaccines appear, based on epidemiology, to trigger GBS, it appears that something specific to the influenza virus or the immune response to that virus causes the immune system to attack myelin. Sivadon-Tardy, Pet. Ex. 45, at 53-55.

In many respects, Dr. Pike's theories, particularly his molecular mimicry theory, are in conflict with his opinion that all the vaccines contributed, as did William's intercurrent illness, to his development of GBS. The molecular mimicry theory, as

pertaining to causation of GBS, requires that the immune system begins attacking the myelin sheaths of peripheral nerves because something in the vaccines caused the immune system to recognize myelin of the peripheral nerves as an invader. The essence of this process requires something specific in a vaccine that resembles some part of the myelin sheath such that the immune system activates and targets myelin instead of or in addition to activation to fight the disease against which the vaccine was administered. Thus, it is unlikely that all the vaccines contain something that bears a sufficient relationship to myelin so as to cause the body to attack itself.

When a biological mechanism cannot be demonstrated, we look to other evidence that suggests a vaccine, infection, or toxin triggers or causes a condition. For example, it is widely recognized that smoking causes lung cancer, but the precise biological mechanism by which it does so remains unknown. Scientists (and courts) have accepted this causal relationship based on epidemiologic evidence, even in the absence of biological or direct mechanistic evidence for how smoking does so. Similarly, most of the referenced articles appear to accept that some versions of influenza vaccine produce more cases of GBS than would be present in the general population in the absence of vaccination.[59] *See, e.g.*, Haber (2004), Pet. Ex. 17, at 2480 (noting extensive variability in reporting rates of GBS following flu vaccines); Lasky, Pet. Ex. 21, at 1797 (reporting slightly increased risk in some years, and no increased risk in others).

Petitioner has the burden to present a reliable and reputable medical theory, which must be "legally probable, not medically or scientifically certain." *Knudsen*, 35 F.3d at 548-49, *Daubert,* 509 U.S. at 590 (holding that scientific evidence and expert opinions must be reliable to be admissible). If there is no reliable evidence that any of the vaccines William received can cause GBS because there is no evidence that they actually do so, the theories become irrelevant. In the next subsection, I examine the evidence that any vaccine William received can or does cause GBS.

[59] However, at least two of the filed journal articles suggested, as did Dr. Feinberg (Tr. at 114-15), that even if the influenza vaccine can cause GBS, the result of vaccinating large groups against influenza may reduce the overall incidence of GBS. Juurlink, Pet. Ex. 18, at 2219-20 (noting a year to year variability in association between influenza vaccines and GBS in the medical literature, finding a statistically significant temporal association between influenza vaccine and hospital admissions for GBS in 2004, but failing to find any increase in the incidence of GBS in the overall population in spite of a mass influenza vaccination program in 2000); Sivadon-Tardy, Pet. Ex. 45, at 55 (noting that another study had shown a protective effect against GBS from influenza vaccinations).

c. Evidence of Causality for Individual Vaccines.

Regardless of the theory on which petitioner relies, his difficulty in proving causation is that the mechanistic evidence in the peer reviewed medical literature is weak, as it consists largely of case reports and some associations between GBS and the natural infections against which these specific vaccines are administered.[60] Furthermore, Dr. Feinberg testified that the case reports associating GBS with the vaccines that William received "don't add up to even a fraction of the cases that have been associated with viral illnesses or *campylobacter jejuni*." Tr. at 96. In contrast to Dr. Pike's causation assertions, the epidemiological evidence suggests that the vaccines William received are unlikely to cause GBS, particularly in light of evidence showing that the reported rates of GBS after any vaccine that William received do not exceed the background rates of GBS. I conclude that petitioner has failed to establish that any of these vaccines can cause GBS.

The evidence for causation by the tetanus component of the Tdap vaccination, is discussed separately in light of the conflicting conclusions reached by the 1994 and 2011 IOM reports. Like the 2011 IOM Report and Dr. Feinberg, I conclude that the evidence that tetanus vaccine can cause GBS is lacking.

An examination of the evidence supporting the first *Althen* prong—whether specific vaccines can cause or trigger GBS—follows. Then, below in section IV.C.4, I return to Dr. Pike's primary theory—that all the vaccines, acting together with William's intercurrent respiratory infection caused his GBS—and look for logical reasons to conclude that they did so.

(1) IPV and Varicella: No Supporting Evidence.

With regard to the IPV[61] and varicella vaccines, petitioner produced no evidence other than Dr. Pike's opinion and VAERS data to demonstrate that these vaccines can cause GBS. The lack of reliability of VAERS data in general and Dr. Pike's use of it in

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[60] I recognize that petitioners cannot be required to produce epidemiologic studies in order to establish causation. *Capizzano*, 440 F.3d at 1325 (holding that such studies cannot be required to show a logical sequence of cause and effect, the second of the Althen prongs). However, when epidemiologic studies exist and such studies find no evidence for a causal relationship, a "special master can consider [the studies] in reaching an informed judgment as to whether a particular vaccination likely caused a particular injury." *Andreu v. Sec'y, HHS,* 569 F.3d 1367, 1379 (Fed. Cir. 2009); *see also W.C. v. Sec'y, HHS*, 704 F.3d 1352, 1360-67 (Fed. Cir. 2013); *Taylor v. Sec'y, HHS*, 108 Fed. Cl. 807, 819-21 (2013).

[61] Other than Dr. Pike's VAERS research, the only evidence of a possible causal role of the polio vaccine concerned the oral polio vaccine. Haber (2009), Pet. Ex. 36, at 314-15. William received the inactivated polio vaccine, a different type of vaccine.

particular have been addressed above. I do not find reliable evidence that either vaccine can cause GBS.

(2) Hepatitis A and MMR: Case Reports Plus Natural Infection.

Case reports[62] primarily consist of published articles reporting a temporal association between an antecedent event and an illness or injury. A case series consists of more than one case report of such an association. As proof of a causal relationship between a vaccine and an illness, case reports are extremely weak evidence. This is because they describe a temporal relationship between a vaccine and an injury, which, standing alone, does not constitute preponderant evidence of vaccine causation. *See*, *e.g.*, *Veryzer v. Sec'y, HHS,* 100 Fed. Cl. 344, 356 (2011) (explaining that "a temporal relationship alone will not demonstrate the requisite causal link and that petitioner must posit a medical theory causally connecting vaccine and injury"). The *Reference Manual on Scientific Evidence*, Federal Judicial Center, 2011(3d ed.) at 724, notes that, in determining medical causation, case reports "are at the bottom of the evidence hierarchy," largely because they lack controls and thus do not provide the level of information or detail found in epidemiologic studies. *See also* Haber (2009) Pet. Ex. 36 at 319 (noting that case reports are of limited value for causality assessments).

Case reports, VAERS reports, and some mechanistic evidence based on a possible association between natural infection and GBS constitute the only evidence supporting Dr. Pike's opinion for the causal role of the hepatitis A and MMR vaccines. Additional inquiries, including epidemiologic studies[63] and comparison of the reported VAERS cases to the background rate of GBS, strongly suggest that these case reports are coincidental rather than causal.

(i) Hepatitis A.

Doctor Pike's supplemental report mentioned case reports of GBS following hepatitis A vaccination, studies involving the vaccine, and the association between natural hepatitis A infections and GBS. Pet. Ex. 14 at 2-3. He asserted that the initial hepatitis A vaccination was among those "most likely implicated" in the development of

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[62] Doctor Pike defined a case report as "a form of epidemiologic study." Tr. at 27. However he later acknowledged that the IOM classified case reports as "mechanistic evidence." Tr. at 62. Doctor Feinberg testified that case reports do not qualify as epidemiologic studies. Tr. at 97.

[63] I recognize that epidemiologic studies cannot "rule out" causation in any particular case. They cannot prove a negative association. However, as compared to case reports, an epidemiologic study showing no association is, in general, more compelling evidence that the vaccine was not likely causal.

William's GBS. Pet. Ex. 10 at 7. He included the second hepatitis A vaccine as among those "implicated independently as substantial causal factors." *Id.* at 8.

Petitioner also filed a review article concerning hepatitis A virus ["HAV"] infections and vaccines, but it does not support a causal role for the hepatitis A vaccine. *See* Pet. Ex. 47, J. Stübgen, *Neuromuscular complications of hepatitis A virus infection and vaccines*, J. NEUROL. SCI. 300: 2-8 (2011). The abstract sums up the article's conclusions, which are contrary to Dr. Pike's causation claims:

> Epidemiological data also cast doubt on the importance of HAV as a trigger for Guillain-Barré syndrome. . . . Isolated case histories report on an unconvincing association between HAV vaccination and neuropathy. Medical and epidemiological data show insufficient evidence to support a causal relationship between HAV vaccines and neuropathy syndromes. . . . This review concludes that it seems unnecessary to routinely consider HAV infection or vaccination as triggers of neuromuscular diseases.

Id. at 2. I thus conclude that petitioner has failed to meet the first *Althen* factor with regard to this vaccine.

(ii) MMR Vaccine.

Doctor Pike's assertions regarding the MMR vaccine's causal role were somewhat inconsistent. He identified the egg protein content of this vaccine with reference to his P2 protein causation theory. Tr. at 15. I consider this theory unreliable, based on the reference cited for it. *See supra* at n.56. However, Dr. Pike also identified molecular mimicry as the most likely mechanism by which the MMR vaccine could induce autoantibodies causing GBS. Tr. at 11, 13-14. He also asserted that "the literature" reported that MMR vaccine was capable of producing GBS (Tr. at 22), but he did not cite to any specific sources for this assertion, either in testimony or expert reports.[64] I have considered the VAERS research data pertaining to the MMR vaccine and GBS and conclude that it is not reliable evidence that this vaccine can or does cause GBS.

The remaining evidence contradicts or severely weakens Dr. Pike's assertions regarding the MMR vaccine and causation of GBS. The Haber 2009 literature survey noted two case reports of GBS occurring one week after measles vaccination and three

[64] Doctor Pike testified that if his report did not contain a specific citation to an article discussing MMR-caused GBS, his inclusion of it as a causal vaccine was either based on his general knowledge or a reference in one of the endnote citations within an article he cited. Tr. at 84-85.

cases of GBS reported following a mumps vaccine. The authors commented that these reports were "uncontrolled observations," and the lack of detail provided "precludes determination of a causal relationship." Pet. Ex. 36 at 316-17.

Furthermore the authors reported that surveillance of adverse events following a mass measles vaccination program involving 70 million children in South America found no excess risk of GBS. The number of GBS cases reported did not exceed the background rate. *Id.* at 317. Additionally, they reported that two MMR vaccine studies in Finland failed to show an increased risk of GBS post-vaccination. *Id*.; *see also* 2011 IOM report, Res. Ex. I, at 165-66 (indicating that GBS had been described in case reports following wild-type measles infections and following measles and mumps vaccinations, but noting flaws in the publications and deeming them "weak" mechanistic evidence and inadequate to support a causal relationship between MMR vaccine and GBS).

The evidence produced fails to establish that either the hepatitis A vaccine or the MMR vaccine can cause GBS, and thus petitioner has failed to meet *Althen's* first prong with regard to either vaccine.

(3) Meningococcal Evidence.

The only evidence suggesting a causal relationship between the meningococcal vaccine William received and GBS was a news release from the U.S. Food & Drug Administration dated September 30, 2005, filed as Pet. Ex. 49. The news release reported five cases of GBS following administration of the meningococcal vaccine that William received, and indicated "[i]t is not known yet whether these cases were caused by the vaccine or are coincidental." No additional information was filed.

This news release, coupled with Dr. Pike's assertions and VAERS research, does not constitute preponderant evidence that the meningococcal vaccine can cause GBS, particularly in light of the absence in the ensuing seven years of any case reports, studies, or other evidence suggesting that the spike in cases was more than coincidence. Furthermore, a 2008 study based on a mass meningococcal vaccination campaign in Canada showed no increased risk of GBS within eight weeks of vaccination. Haber (2009), Pet. Ex. 36, at 316 citing P. De Wals, et al., *Risk of Guillain-Barré syndrome following serogroup C meningococcal conjugate vaccine in Quebec, Canada,* CLIN. INFECT. DIS. 46(8): e75-7 (2008). I thus conclude there is inadequate evidence that the meningococcal vaccine can cause GBS.

(4) Tetanus Vaccine and 1994 IOM Report.

A substantial portion of the testimony by Dr. Pike was devoted to his attempts to demonstrate a causal relationship between the tetanus vaccine and GBS. Tr. at 20-23,

25-26, 59-61, 64-65. Relying on the 1994 IOM report, which had concluded that the evidence favors the existence of a causal connection between tetanus toxoid and GBS,[65] Dr. Pike claimed that a causal relationship between tetanus vaccine and GBS had been demonstrated and that the timing between William's tetanus vaccine and his GBS was consistent "with known intervals for the development of Guillain-Barré either in wild form, wild type in nature, or post-vaccination." Tr. at 10, 19-21. At the same time, he declined to rely absolutely upon the IOM as the "sole arbiter" of causality. Tr. at 20. Petitioner also filed two case reports of tetanus following GBS. *See* Pet. Exs. 30 and 31.

Doctor Pike's ambivalence towards the IOM may be explained by the 2011 IOM report, Res. Ex. I. The 2011 IOM committee altered the IOM's 1994 position on a causal relationship between tetanus vaccine and GBS, concluding that epidemiologic evidence[66] was insufficient to demonstrate a causal association between tetanus toxoid and GBS. 2011 IOM Report, Res. Ex. I, at 557. More significantly, it found even the mechanistic evidence lacking, finding that the case reports described only temporal connections, with some of the reports describing onset in periods too long or too short for the possible causation mechanisms. *Id.* at 557-58.

One well-documented case report from 1978, Pollard and Selby,[67] on which the 1994 IOM committee had relied, is missing from the tetanus and GBS section of the 2011 Report. The patient in this case study had experienced GBS-like symptoms after successive tetanus vaccinations, and based on this challenge-rechallenge evidence,[68] the 1994 IOM committee had concluded that tetanus vaccine could cause GBS. 1994

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[65] Pet. Ex. 26 at 89. The report noted that the committee believed the incidence or relative risk would be low, but that they were unable to provide an estimate because their conclusion did not rely on controlled studies.

[66] This evidence included one study (N. Souayah, et al., *Guillain-Barré Syndrome after Vaccination in United States: Data from the Centers for Disease Control and Prevention/Food and Drug Administration Vaccine Adverse Event Reporting System (1990-2005)*, J. CLIN. NEUROMUSC. DISEASE 11(1): 1-6 (2009), filed as Pet. Ex. 46. As the title indicates, this study was based on VAERS data. As the IOM 2011 Committee noted, it also lacked an unvaccinated comparison population, rendering this study's conclusions poor evidence of causality.

[67] This case report was not filed as an exhibit, but it was extensively discussed in testimony (Tr. at 25-27, 105-06), and in other exhibits filed, including the 2011 IOM discussion. *See, e.g.*, Haber (2009), Pet. Ex. 36, at 315.

[68] Challenge-rechallenge refers to a situation where an individual is exposed to a vaccine or antigen and has a reaction, and then is exposed to the same item and suffers a similar reaction. The 2011 IOM report stressed that greater value is placed on rechallenge case reports occurring in monophasic conditions than in relapsing-remitting conditions. 2011 IOM Report, Res. Ex. I, at 46-47.

IOM Report, Pet. Ex. 26, at 89 ("[B]ecause the case by Pollard and Selby (1978) demonstrates that tetanus toxoid *did* cause GBS, in the committee's judgment tetanus toxoid *can* cause GBS.").

However, later events cast doubt on the diagnosis of GBS in the Pollard and Selby case report. One of the original authors reported that the case study patient had experienced GBS-like symptoms after other immune challenges, such as acute viral infections. 2011 IOM report, Res. Ex. I, at 559; Haber (2009), Pet. Ex. 36, at 315. This, coupled with the recognition that Chronic Inflammatory Disseminated Polyneuropathy ["CIDP"] was a disorder different from GBS,[69] convinced the 2011 IOM committee to move discussion of the Pollard and Selby case study from the section on GBS to the following section dealing with vaccinations and CIDP. 2011 IOM report, Res. Ex. I, at 559. Thus, the Pollard and Selby case study, which had provided the strongest evidence for causality in the 1994 report, was considered to be a case of CIDP, rather than GBS, and could not serve as evidence for tetanus vaccine causation of GBS in the 2011 IOM report.

The need to differentiate between CIDP and GBS diagnoses in studying GBS after vaccination was discussed in Juurlink, Pet. Ex. 18, at 2218 (describing the methods used to avoid counting CIDP cases as GBS cases). This supports Dr. Feinstein's testimony that they are considered different syndromes with different clinical courses and causes. *See also* Haber (2009), Pet. Ex. 36, at 319-20

Doctor Pike also attacked the 2011 IOM Report's changed conclusion by a contention that the 2011 IOM committee required conclusive proof of vaccine causation.[70] Tr. at 24-25. He disagreed that the Pollard and Selby case was excluded

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[69] By definition, GBS is monophasic, meaning it occurs only once. In contrast, CIDP reoccurs. In initial presentation, patients with CIDP are often difficult to distinguish from patients with GBS, as the initial symptoms are very similar. However, GBS typically responds to either plasma exchange or IVIG; patients with GBS who receive steroids typically do not improve or may get worse. Patients with CIDP generally improve on steroids. Tr. at 104-07, 123-24; *see also* Ropper & Samuels, NEUROLOGY, at 1292-93.

[70] The 2011 IOM report discusses how both epidemiologic and mechanistic evidence were assessed to determine whether vaccines play a causal role in the adverse events occurring after vaccination. 2011 IOM Report, Res. Ex. I, at 39. Epidemiologic studies were assessed for methodological limitations, confounding variables, and precision of results, among other factors. *Id.* at 43. Mechanistic evidence, as defined in the 2011 IOM report, included some epidemiological studies where the study design limited the conclusions that could be drawn, as well as case reports, evidence of a pathophysiological process reasonably likely to cause an adverse event, evidence of rechallenge (particularly those involving monophasic conditions), a work up that ruled out other causes, the isolation of vaccine strain virus from the patient, and the effects of natural infection. The 2011 IOM committee used the following categories in assessing the weight of mechanistic evidence: (1) strong (defined as "[o]ne or more cases in the literature, for which the committee concludes the vaccine *was* a contributing cause of the adverse event"); (2) intermediate (defined as "[a]t least two cases . . . for which the committee concludes the vaccine *may*

because it represented CIDP, not GBS. Tr. at 27. Doctor Pike suggested that the IOM committee was motivated to exclude it because the "Health Care Finance Administration has demanded that they use only evidence-based approaches." Tr. at 27-28. I note that the Haber 2009 article, Pet. Ex. 36, at 319-20, suggested that the IOM reexamine its 1994 report's conclusions regarding challenge-rechallenge evidence[71] based on the Pollard and Selby article in view of the patient's relapsing course in response to other immune stimuli. I have carefully read the entire 2011 IOM report, and I find no support for Dr. Pike's contention. He either misinterpreted comments taken out of context or misunderstood the role of the 95% confidence interval in epidemiology.

I note that the role of the IOM is to examine and reexamine vaccine safety. § 1 (requiring the Secretary of HHS to consult with the IOM regarding vaccine safety); *see also* 2011 IOM Report, Res. Ex. I, at 29-30. A review of a prior conclusion in light of new information is not evidence that the IOM is "cracking down" on causality determinations. I also note that the 2011 IOM committee added adverse events associated with vaccination on its own initiative, based on evidence that had developed in the investigatory process. *Id.* at 36.

Notwithstanding the lack of evidentiary support for Dr. Pike's assertions, the 2011 IOM may have required a higher burden than "preponderant evidence" of vaccine causation before concluding that the evidence convincingly supports a causal relationship or favors acceptance of a causal relationship.[72] *Id.* at 42. I have applied a preponderance of the evidence standard in evaluating the IOM's conclusions. Nevertheless, I find insufficient evidence to demonstrate that tetanus vaccine can cause GBS. Assuming, *arguendo*, that tetanus vaccine can cause GBS, I find insufficient evidence that it did so, as detailed in section IV.C.5 below.

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be a contributing cause of the adverse event"); (3) low-intermediate (defined as "at least two cases . . . while suggestive, are nonetheless insufficient for the committee to conclude the vaccine may be a contributing cause of the adverse event"); (4) weak (defined as "insufficient evidence"); and (5) lacking evidence of a biologic mechanism. *Id*. at 48 (emphasis original).

[71] The 2011 IOM report noted the importance of challenge evidence in assessing case reports, but noted that each report of challenge in the same patient must meet the same reliable criteria in terms of timing and documentation of both vaccine and adverse event. Res. Ex. I at 46-47.

[72] For example, the 2011 IOM committee indicated that it was unlikely to accept one epidemiological study, no matter how well designed, as sufficient for a conclusion that the vaccine studied was causal. 2011 IOM Report at 17. The committee explained that one study should be viewed with caution, due to an inability to judge consistency of results. *Id.* This is consistent with the *Daubert* factor of "error rate" in evaluating scientific evidence for admissibility. *Daubert*, 509 U.S. at 594. Notwithstanding the IOM's approach, one well-designed epidemiological study indicative of vaccine causation could support a Vaccine Program determination that the first *Althen* prong had been met.

(5) Non-Covered Vaccines.

When I asked Dr. Pike to rank the vaccines in terms of which one was most likely to be responsible for William's GBS, the first vaccine he identified was the yellow fever vaccine. He testified that it "is very suspicious to me." Tr. at 66-67. He opined that the yellow fever vaccine "could have played a role" in William's GBS. Tr. at 9-10. He based his opinion on the "very high content of egg protein" in the vaccine and studies on animal models. Tr. at 9, 15-16. Aside from the Geier study, Pet. Ex. 34, there was little evidence buttressing his testimony. He also relied on his own VAERS research, testifying that although the yellow fever vaccine comprised 4% of the vaccines administered, it comprised a significantly higher percentage of the reports of GBS following vaccine. Tr. at 67-68; *see also* Pet. Ex. 14 at 11-13.

Doctor Pike did not include any case reports or studies related to yellow fever vaccine and GBS. Doctor Pike also testified that he was unaware if GBS was linked to yellow fever infections. Tr. at 69. However, the Haber 2009 article, Pet. Ex. 36, at 318 reported six cases of GBS in the VAERS database that had occurred within 30 days of receipt of a yellow fever vaccine. The same article also described other studies covering the period between 1990-2004, which found five cases of GBS after yellow fever vaccine. By comparing the reporting rate (1.9 cases within 30 days of vaccine per million doses distributed in the U.S.), to the background rate of GBS (0.8-3.3 cases per 30 days per million population), they found no elevated risk of GBS after yellow fever vaccine. Pet. Ex. 36 at 318. The authors also noted that a U.K. study also found that the risk of GBS after yellow fever vaccination did not exceed the expected background rate of GBS. *Id*.

Of course, even if Dr. Pike is correct in his assertion that the yellow fever vaccine is the vaccine most likely to have caused William's GBS, he has torpedoed petitioner's causation case. Yellow fever vaccine does not appear on the Table, and if it is the most likely culprit, petitioner cannot prevail.

Although Dr. Pike included the adult pneumococcal vaccine in his group of vaccines most likely to be causal (which includes all of the July 23 vaccinations), he did not provide much testimony or other evidence concerning its causal role. He lumped it with the other vaccines in his reports (Pet. Exs. 10 at 7; 14 at 3) and in his testimony (Tr. at 16). When he discussed it at all in his testimony, it was to suggest that William's sore throat might have been the result of streptococcal pharyngitis, which "is related to the pneumococcus," referring to the causal organism for the pharyngitis. Tr. at 18. From context, it is difficult to understand if Dr. Pike was saying that William's sore throat was the result of his pneumococcal vaccine or simply that the organism against which this vaccine is administered could cause sore throats and thus could be a cause of William's illness. If Dr. Pike was saying that this vaccine was likely causal, such a

statement would undercut petitioner's causation case, as the adult pneumococcal vaccine is not a Table vaccine.

d. Summary.

William received two doses of Twinrix (hepatitis A and B), and one dose each of MMR, varicella, IPV (polio), meningococcal, and Tdap, which are all vaccines appearing on the Table. He also received two vaccines (yellow fever and adult pneumococcal) not appearing on the Table. Doctor Pike testified that the hepatitis B vaccine did not play a causal role and petitioner produced no evidence regarding IPV and varicella. There was insufficient reliable evidence that any of the remaining Table vaccines can cause GBS. If Dr. Pike were correct in his assertion that the yellow fever vaccine was the most likely culprit in causing William's GBS, the likelihood that any Table vaccine caused his injury is even further removed from consideration.

I conclude that there is insufficient evidence that any of the vaccines William received can individually cause GBS. Because Dr. Pike asserted that all of the vaccines William received could, alone or in connection with his upper respiratory infection, cause his GBS, it is necessary to examine whether these vaccines could collectively do what they could not do on their own.

4. *Althen* and the Combined Effect Theory

a. Theory

In asserting that all of William's vaccines contributed to his development of GBS, Dr. Pike simply relied on his own experience. Tr. at 18-19, 21-22, 41-42. What specific experiences led him to this conclusion were not elucidated. In a general statement regarding how they did so, Dr. Pike referred to "mechanisms by which infection, inflammation, and vaccination are believed to induce an exaggerated, enhanced, and aberrant immune response." Pet. Ex. 14 at 1. Likewise, his statement that "[v]accinations are relatively contraindicated when an individual is suffering from an active infection because of the greatly increased risk of triggering an immunologically mediated vaccine caused adverse effect" (Pet. Ex. 10 at 21; *see also* Tr. at 42-43) was unsupported by any evidence.[73]

In contrast, Dr. Feinberg testified that there was no evidence that vaccines work synergistically to cause GBS. Tr. at 93, 102, 125-26. While I could simply accept Dr.

[73] I have found that William was not actively ill at the time he received either set of vaccinations. *See supra* at Section III.B. At best for petitioner's causation theory, William had some lingering symptoms, but it is more likely that they were attributable to his chronic sinusitis.

Feinberg's statements as more likely correct, in view of his greater expertise in GBS cases,[74] there are several pieces of evidence that buttress this testimony.

First, Dr. Pike's combined effects theory is mentioned nowhere in the medical literature. Second, it runs contrary to the molecular mimicry theory of how GBS is caused. That theory requires something other than general immune activation; it requires an immune system attack on the body's own cells in a case of mistaken identity. This is inconsistent with Dr. Pike's broad-based immune stimulus causation theory. Third, the theory that the many vaccines produced an exaggerated immune response conflicts with how the vast majority of cases of GBS occur. Over two-thirds follow a mild upper respiratory or gastrointestinal illness and most of the remainder of cases occur without any known antecedent illness. Thus, there is no evidence that hyperstimulating the immune system produces GBS.

Although circumstantial, these factors convince me that Dr. Pike's theory is not reliable. Other than Dr. Pike's *ipse dixit*, there is no evidence that the combined effects of two sets of vaccines, with or without an acute illness, can cause or trigger GBS.

b. Logical Connection and Alternative Cause

There is also ample evidence that the vaccines did not cause GBS in this case, because the clear weight of the evidence is that William's upper respiratory infection, documented as existing 16 days[75] prior to onset of his GBS symptoms, is a sufficient cause for the GBS. Respondent had no obligation to prove alternate case because a petitioner does not automatically shift the burden to respondent merely by offering an opinion of a medical expert. In *de Bazan*, the Federal Circuit explicitly stated that the special master may consider all of the evidence presented, including that of respondent, in determining whether petitioners have met their burden of proof. 539 F.3d at 1353-54.

Both experts acknowledged that upper respiratory infections can cause GBS. Although Dr. Pike discounted a direct causal role for William's upper respiratory

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[74] *See Locane v. Sec'y, HHS*, 685 F.3d 1375, 1380 (Fed. Cir. 2012)(finding nothing arbitrary or capricious about a Special Master finding one expert's testimony more persuasive than another because of the experts "different backgrounds and specialties and because the medical literature support[ed]" the one expert's theory).

[75] At the hearing, Dr. Pike could not recall precisely when William first presented to sick call with respiratory symptoms, but asserted that it was "six days or so" before his GBS symptoms manifested. Tr. at 44. When shown the medical record, he agreed that the symptoms were first reported to a health care provider on August 9, which was 16 days before onset of GBS symptoms. Tr. at 46-47.

infection because the exact nature of the infection is unknown,[76] he agreed that respiratory infections can cause GBS. Tr. at 51, 66; *see als*o Pet. Ex. 14 at 9. The medical literature Dr. Pike referenced in his expert reports also supported a causal role for upper respiratory infections. *See, e.g*., Sivadon-Tardy, Pet. Ex. 45, at 48 (60-70% of GBS patients report a recent upper respiratory infection or gastrointestinal illness). The epidemiologic evidence that upper respiratory infections play a significant causal role in many, if not most, cases of GBS did not focus on the nature of the pathogen causing the infection, merely that they were present a few weeks prior to onset of GBS in many patients.

Doctor Feinberg opined that the vaccines William received were not responsible for his GBS. He testified that "overwhelmingly the most common cause or prodrome associated with Guillain-Barré is an upper respiratory tract infection." Tr. at 93 He added that *C. jejuni* is the most commonly identified bacterial organism, but that viral infections are the most common cause. Tr. at 94. He based his opinion on the lack of reliable evidence that any of the vaccines received could cause GBS, much less that they did so in William's case. Res. Exs. B (Expert Report) at 3, H (Supplemental Expert Report) at 2; *see also* Tr. at 96-97. He testified:

> [I]t would be nice if you could ignore the fact that [William] was sick and that he'd just had all these vaccinations, and then got Guillain-Barré syndrome. But the fact of the matter is that he was sick. He was seen by health care providers on two occasions, and he clearly had some sort of illness. In my opinion, it doesn't really matter what type of illness he had, whether it was bacterial strep throat, flu, a cold, a common cold, the fact of the matter he was sick, and the fact of the matter is that he being sick is far more likely to be associated with Guillain-Barré syndrome than any of these vaccines.

Tr. at 116-17.

In his second report, Dr. Pike contended that Dr. Feinberg was incorrect in drawing a causality conclusion about the greater role of infections in GBS because there are many more infections than there are vaccinations, and infections have existed much longer than vaccinations. Pet. Ex. 14 at 15. He stated:

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[76] Tr. at 21 ("[W]e don't know what the respiratory infection was, we don't know anything at all about it, so that's kind of a speculative issue since we have very little information about it. We don't know whether it was a streptococcal infection, we don't know whether it was a viral infection, we don't know if it was influenza. So that all has got very little probative value, at least in my mind, other than to say [William] had an upper respiratory infection . . . .); *see also* Tr. at 18, 76.

> Thus it is abundantly clear that there has not been the same opportunity for vaccine associated GBS to be recognized and reported as there has been with regard to infection related GBS (*Campylobacter jejuni* the most commonly cited infection preceding GBS and not viral upper respiratory infections). Furthermore, the population at risk for infection and the development of post-infection GBS is over six billion today compared to a much smaller population at risk that receives vaccines, a thousand-times less (millions compared to billions). The number of published reports of infection related GBS is not a measure of the actual risk of GBS following infection. In fact, large studies [of] populations that have received influenza vaccines have shown the risk of post-vaccine GBS to be higher than background (natural rate of spontaneous GBS plus post-infectious GBS).

Id. at 15-16. This paragraph contained no citations to any authority.

While it is true that many more illnesses occur than vaccinations, these statements ignore the fact that most GBS patients report an antecedent illness. Furthermore, mass influenza vaccination programs appear to reduce cases of GBS, indicating that influenza virus is more likely a cause than influenza vaccine. The only vaccine demonstrated to cause a significantly increased risk of GBS (four to eightfold over background rate) was the 1976-77 swine flu vaccine. The increased risk of GBS after other influenza vaccines is estimated to be 1-2 per million doses of vaccine. Lasky, Pet. Ex. 21, at 1800-01. For purposes of analyzing the increased risk, this study presumed that any case of GBS occurring in the six weeks following an influenza vaccine was vaccine caused. They found that evidence of other causes was much less common in patients that had received vaccines. *Id*. Interestingly, they found no "vaccine associated cases" in the 4,000,000 patients under 45 years of age. *Id*. Based on the preliminary findings of this study, the Advisory Committee on Immunization Practices noted that even with an increased GBS risk of 1-2 per million vaccinated, this increased risk is less than the risk associated with influenza disease. *Id*. at 1801.

A known risk for GBS was present in this case. Upper respiratory infections are a widely recognized trigger for GBS,[77] a fact conceded by Dr. Pike. This infection was, medically and legally, a sufficient cause for developing GBS. At best, the vaccine associated risk is speculative.

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[77] *See, e.g.,* Haber (2009), Pet. Ex. 36, at 310-11 ("About two-thirds of GBS cases occur several days or weeks after an apparent infectious illness, commonly a diarrhoeal illness or upper respiratory tract infection."); Sivadon-Tardy, Pet. Ex. 45, at 48 ("GBS occurs after acute infectious disease (usually respiratory tract infection or gastrointestinal illness) in 60-70% of patients."); Rees, Res. Ex. F, at 1374 ("In approximately two thirds of patients, neuropathic symptoms follow an infection – often a mild, undiagnosed respiratory or gastrointestinal illness.").

5. Timing: Too Soon, Too Late, and Just Right.

Assuming, *arguendo*, that petitioner satisfied the first two *Althen* prongs, he still fails on the third prong, that of a medically appropriate temporal relationship. The requirement to demonstrate an appropriate temporal connection necessitates a showing that the injury occurred in a medically or scientifically reasonable period of time after the vaccination, not too soon (*see de Bazan*, 539 F.3d at 1352) and not too late (*see Pafford*, 451 F.3d at 1358). However, a proximate temporal connection between a vaccination and an injury is insufficient, standing alone, to establish causation. *Grant*, 956 F.2d at 1148. A proximate temporal relationship, even when coupled with the absence of any other identified cause for the injury, is not enough to demonstrate causation under the Vaccine Act's preponderance standard. *Moberly,* 592 F.3d at 1323 (citing *Althen*, 418 F.3d at 1278).

As indicated earlier, much of Dr. Pike's own flawed research focused on timing. He also cited another study that looked at VAERS data pertaining to GBS for this point, but took the quotation out of context.[78] Doctor Pike's report reflects the following: "They [referring to the study's authors] consider any case occurring in the first six weeks after vaccination to be 'more likely to have been causally related to vaccination.'" Pet. Ex. 10 at 16 citing to Haber (2004). This formulation suggests that the Haber authors were saying that any case of GBS occurring within six weeks of any vaccine was caused by the vaccine. However, the "more likely" quotation refers to a subset of all the influenza cases examined, which were separately examined in an effort to improve the quality of the VAERS data, not a causality determination related to any vaccine and GBS. The Haber (2004) study actually concluded:

> [T]he long onset interval and low prevalence of other preexisting illnesses are consistent with a possible causal association between GBS and influenza vaccine. These findings require additional research, which can

[78] The article was Haber (2004), filed as Pet. Ex. 17. The study compared reporting rates of GBS following influenza with reporting rates for other illnesses, finding a median onset interval in influenza-GBS cases of 13 days. In addition to the VAERS reports, the authors "conducted active follow up of all GBS reports following influenza vaccination to verify the diagnosis and to obtain additional clinical information (eg, prior illness within 4 weeks before onset of GBS, history of prior influenza vaccination, and prior GBS occurrence)." *Id.* at 2479. Thus this study eliminated one of the problems with reliance on VAERS data by confirming diagnosis. However, I do not rely on this study to establish a medically appropriate temporal interval between vaccine and onset; I reference it only to demonstrate Dr. Pike's misinterpretation of the study's use of a six week interval for consideration in examining the relationship between influenza and GBS. He presumed that it meant any case of GBS occurring within six weeks was vaccine caused, when the study participants used the six week period as an outer limit for cases that could be vaccine caused.

> lead to a fuller understanding of the causes of GBS and its possible relationship with influenza vaccine.

P. Haber (2004), Pet. Ex. 17, at abstract.[79] The "long onset interval" refers to the longer median onset interval of 13 days associated with reports of GBS after influenza vaccines compared to the onset interval of 1 day for non-GBS adverse events following a flu vaccination. Pet. Ex. 17 at 2480.

Onset time was a significant factor in the 1994 IOM Report's causality analysis. With regard to GBS, the 1994 IOM concluded that five days to six weeks was a temporally appropriate time period. Pet. Ex. 26 at 87. The time frame was computed as follows:

> [T]he expected latency between an antecedent event (when infection or administration of antigen occurs) and the first symptoms of GBS is mainly between 7 and 21 days. Occasional cases appear to have latencies of between 22 and 42 days. All evidence indicates that GBS is immune mediated via a delayed-type hypersensitivity mechanism. Taken together, these two observations allow a range of latencies to be stated for GBS, that is, 5 days to 6 weeks.

Id. at 45.

Unfortunately for petitioner, the same 1994 IOM Report he relies upon for causality with regard to the tetanus vaccine takes that vaccine, as well as the yellow fever vaccine, out of the running, based on timing. William received his tetanus and yellow fever vaccines on August 22, four days before he manifested symptoms of GBS.

The July 23 vaccines were received 34 days prior to onset of William's GBS symptoms. Thus, under the 1994 IOM criteria, they are in the ballpark for causation. However, Dr. Pike did not rely on the 1994 IOM criteria for timing; he relied on his own research, placing the peak period for causation for the vaccines William received at between 10-30 days. Pet. Ex. 10 at 14 (Histogram entitled "Percent By Onset Interval and Symptoms"). The July vaccines were received too soon to fall within this peak period, but were within the 60 day outer limit. Pet. Ex. 10 at 15.

The upper respiratory infection, first reported 16 days prior to onset of William's GBS falls squarely within the peak period, per Dr. Pike's 10-30 day window. Pet. Ex. 10 at 14. This initial expert report also indicated that the "greatest relative risk for

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[79] The authors later conducted that follow up study, which was published in 2009 and filed as Pet. Ex. 36.

developing [GBS] after respiratory infection . . . was in the first two weeks post-infection." *Id*. at 13; see also Haber (2004), Pet. Ex. 17 at 2480 (finding a median onset of GBS of 13 days in influenza, with half the cases occurring in the first two weeks). More significantly, it fell well within the period for causation referenced by Dr. Feinberg of "a few days to a few weeks." Tr. at 100. Doctor Feinberg's testimony on timing was well supported by the medical literature filed.

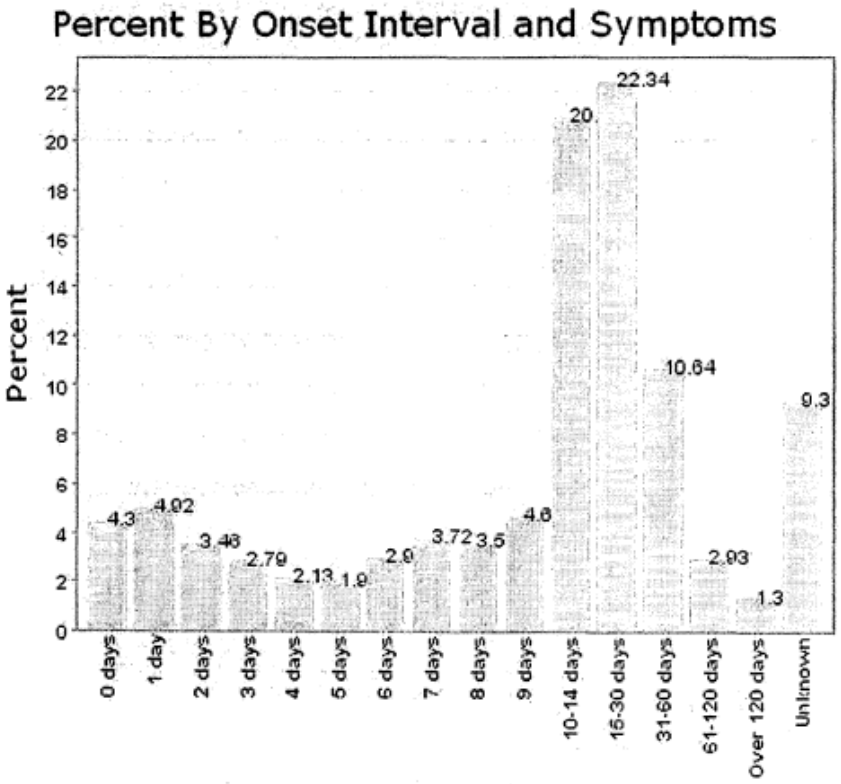
V. Conclusion.

Petitioner has failed to establish any of the *Althen* prongs by preponderant and reliable evidence. He has not demonstrated that his condition was either caused in fact or significantly aggravated by any or all of the vaccines alleged to be causal. The petition for compensation is therefore DENIED. The clerk is directed to enter judgment accordingly.

IT IS SO ORDERED.

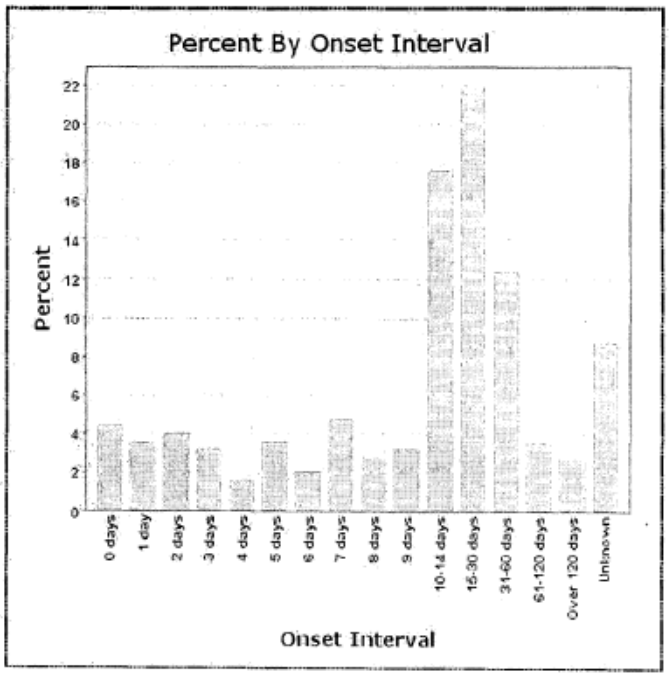
s/Denise K. Vowell
Denise K. Vowell
Special Master

Appendix: Charts from Petitioner's Exhibit 10



Pet. Ex. 10 at 14

EIGHT VACCINE ONSET INTERVAL FOR GBS AFTER INJECTION



Pet. Ex. 10 at 16