In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

YVONNE HARRIS, as Mother and Natural Guardian of KHONSTINCE COUCH, a Minor,	*	No. 10-322V Special Master Christian J. Moran
Petitioner,	*	Filed: June 10, 2014
v.	*	
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Entitlement; human papillomavirus vaccine ("HPV"); lupus.
Respondent.	*	

Michael A. London, Douglas & London, P.C., New York, NY, for petitioner; Ann D. Martin, United States Dep't of Justice, Washington, DC, for respondent.

PUBLISHED DECISION DENYING ENTITLEMENT TO COMPENSATION[1]

Yvonne Harris alleges that her daughter, Khonstince Couch ("Bre"), suffered systemic lupus erythematosus ("SLE") as a result of the human papillomavirus ("HPV") vaccinations that she received on May 30, 2007, and August 1, 2007. Petition at 3-5. Ms. Harris seeks compensation pursuant to the National Childhood Vaccine Injury Compensation Program, 42 U.S.C. §§ 300aa-10 through 34 (2006).

In support of her petition, Ms. Harris relies primarily upon the testimony of Dr. Yehuda Shoenfeld, a specialist in autoimmune disease. Dr. Shoenfeld offered

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

three theories to explain how the HPV vaccine could have caused Bre's lupus. Dr. Shoenfeld's causation theories were opposed by respondent's four expert witnesses: Dr. Carlos D. Rose, a board-certified rheumatologist; Dr. Lawrence D. Frenkel, a board-certified pediatrician, allergist, and immunologist; Dr. Theodore C. Eickhoff, an expert in the field of infectious disease and epidemiology; and Dr. Edward W. Cetaruk, a board-certified medical toxicologist.[2] Background information on each of these testifying experts is discussed below.

This decision is organized into the following sections:

I. Brief Biographies of the Testifying Witnesses

II. Facts

III. Lupus

IV. Procedural History

V. Standards for Adjudication

VI. *Althen* Prong One – Theory

VII. *Althen* Prong Three – Timing

VIII. *Althen* Prong Two – Logical Sequence

IX. Conclusion

As discussed in more detail below, Ms. Harris's claim lacks persuasiveness in two respects. First, she did not establish persuasively that the HPV vaccine can cause lupus. This aspect of her proof is addressed in section VI. below. A second and independent problem is that the evidence showed that Bre was probably suffering from lupus before the vaccination. Thus, the vaccine cannot have caused the disease. The basis for this finding is explained in section VII. below. These two reasons contribute to the finding, in section VIII., that Ms. Harris did not establish a logical sequence of cause and effect between the vaccination and Bre's lupus.

[2] The hearing transcript contains an incorrect spelling (Frankle) of Dr. Frenkel's name.

I. Brief Biographies of the Testifying Witnesses

A. Dr. Shoenfeld

Dr. Shoenfeld graduated from medical school in 1972. In the ensuing 40 years, Dr. Shoenfeld has worked in various capacities, taught at medical schools, conducted research, and authored (at least in part) more than one thousand articles. The breadth of his career is reflected in his 118-page curriculum vitae, which was filed as exhibit 120.

Dr. Shoenfeld's accomplishments are many. The highlights include being awarded, in 2005, the EULAR prize for identifying the infectious etiology of the anti-phospholipid syndrome and being recognized, in 2009, by the Israeli Medical Association for his lifetime contributions to medicine. Exhibit 120 at 8.

Since 1996 (and perhaps earlier), Dr. Shoenfeld has proposed that vaccines contribute to autoimmune conditions. See exhibit 120 at 65, item 625. His recent research has focused on autoimmunity. He founded and still leads the Center for Autoimmune Diseases located within the Sheba Medical Center. Id. at 2. He describes himself as an "autoimmunologist." Tr. 223, 408.

B. Dr. Rose

Dr. Rose graduated from medical school in 1977. He passed his rheumatology board examination in 1983, his pediatric board examination in 1990, and his sub-board examination for pediatric rheumatology in 1998. Exhibit B at 3.

He has taught at Thomas Jefferson Medical College since 1991. During his academic career, he has been promoted from assistant professor to associate professor to professor. Exhibit B at 6. His recent research work has focused on arthritis and lupus. Id. at 18-19.

Dr. Rose sees patients as a pediatric rheumatologist at the Alfred I. duPont Institute of the Nemours Foundation. His patient population is primarily children with rheumatic disorders such as juvenile idiopathic and rheumatoid arthritis, Lyme disease, and connective tissue disorders such as lupus. Tr. 549. He has seen "hundreds" of cases of lupus. Tr. 550.

C. Dr. Frenkel

Dr. Frenkel earned his medical degree in 1969. His early career focused on pediatrics and virology. Exhibit D at 1. In 1983, he became the director of the Division of Immunology, Allergy and Infectious Diseases in the pediatric department of the Robert Wood Johnson Medical School. He held that position for 13 years. Id. He then became a professor in the pediatric department of the University of Illinois, College of Medicine at Rockford. Id. at 2.

Dr. Frenkel is board-certified in pediatrics as well as allergy and immunology. He has a sub-specialty in pediatric infectious diseases. Id.

In 2000 and 2001, he worked on immunization projects in India. Starting in 2008, he has served as co-chair of the New Jersey Immunization Network. Id. at 4.

D. Dr. Eickhoff

When he testified, Dr. Eickhoff held the position of professor emeritus at the University of Colorado, School of Medicine. He attained this position in 2003, which was more than 40 years after he graduated from Western Reserve University School of Medicine. Exhibit O at 1.

Dr. Eickhoff's professional career has centered on infectious diseases and epidemiology. He has served on various committees exploring the safety of vaccines through the Department of Health and Human Services. Id. at 4. For the Institute of Medicine, he participated on a similar committee involving the anthrax vaccine. Id. at 5.

E. Dr. Cetaruk

Dr. Cetaruk graduated from the School of Medicine at New York University in 1991. He received advanced training in emergency medicine. From 1994 to 1996, he had a fellowship in medical toxicology. The American Board of Emergency Medicine recognized him as having special qualifications in medical toxicology in 2000. He became a fellow in the American College of Medical Toxicology in 2009. Exhibit Q at 1-2.

Each expert was provided with Bre's medical history for review. A summary of the relevant medical records is addressed next, followed by a general overview of lupus.

II. Facts

Bre was born in 1998. Bre's mother has a history of atopic dermatitis and asthma, a first-generation cousin suffers from lupus, and her great-grandfather had rheumatoid arthritis. Exhibit 4 at 12; exhibit 3 at 54. This genetic background makes Bre more likely (but not necessarily destined) to develop an autoimmune disease. Tr. 24-26, 192 (Dr. Shoenfeld).

The first filed medical record about Bre was created when she was nine years old. On March 19, 2007, she was seen for a swollen thumb. Exhibit 2 at 1-56; exhibit 26 at 1. Her doctors eventually determined that she was suffering from a methicillin resistant staphylococcus aureas ("MRSA") infection. Id.; see also Tr. 188-89 (Dr. Shoenfeld's discussion of MRSA). In conjunction with this infection, doctors ordered blood tests. Exhibit 2 at 50. Dr. Frenkel cited the results as supporting his opining that Bre was suffering from lupus before vaccination. See section VII., below.

On April 17, 2007, Bre saw Edward J. Vanderburg, who became her primary care doctor. Dr. Vanderburg's examination showed that Bre had a "rash over complete body." Exhibit 26 at 1, 3. Dr. Vanderburg's history of present illness indicates that the rash "has been going off and on for several years. She will get a macular, raised, itchy rash." According to this history, the "[m]ost recent flare up is 2 weeks out." Id. at 3.[3] Dr. Vanderburg assessed Bre as having "[p]robable pityriasis rosea." He prescribed two medications, Bactrim and Keflex, and referred her to a dermatologist. Id. at 1, 3. In testimony, the expert witnesses disputed the significance of the rash. Dr. Rose and Dr. Frenkel linked the rash to Bre's lupus. Tr. 568-70, 616-17, 694-98. Dr. Shoenfeld disagreed. Tr. 31.

Although Bre's mother or cousin had requested a referral to a dermatologist, no record from any dermatologist was filed. Instead, Bre's next encounter with a medical professional was on May 30, 2007, when she received her first dose of the HPV vaccine. The administering entity was the health unit in her local county. Exhibit 1 at 1. There are no records showing Bre's state of health on this date. The same agency administered the second dose of HPV vaccine on August 1, 2007. Id.

[3] The source of information about Bre's history is not entirely clear. On this page of Dr. Vanderburg's note, he states that "Mother wants next treatment plan to come from a dermatologist." Exhibit 26 at 3. However, on a different page, Dr. Vanderburg created an addendum, stating "I was informed later that the woman with the child was the cousin." Id. at 1.

On August 23, 2007, Bre was seen because her "index finger swelling started yesterday." She also had "bright spots all over [her] body." Exhibit 26 at 4. An advance practice nurse saw her and recorded that the rash was on her "face [and] upper extremities," and "spreading." The rash was also "itchy." The nurse assessed her as having "cellulitis and abscess of finger, unspecified" and "allergy, unspecified." The nurse recommended follow up in two weeks. Id.; see also Tr. 571.

Before this follow up appointment took place, Bre developed a fever and headache. Exhibit 25 at 4. On September 9, 2007, Ms. Harris took her to the pediatric emergency department of Arkansas Children's Hospital. Id. at 1-8. The doctor's review of systems indicated that except for Bre's fever, her systems, including her skin, were normal. The doctor's impression was that she had a viral upper respiratory infection and recommended that Bre see her primary care physician in the next two or three days. Id. at 1-4.

On September 11, 2007, Bre was still running a fever. She also had a rash. Therefore, Ms. Harris brought Bre to see Dr. Vanderburg. He found that she had atopic eczema and dry skin on her arms and back. He also diagnosed her with an upper respiratory infection and prescribed an antibiotic and antihistamine. Exhibit 26 at 6-7.

Throughout that night, Bre vomited. She also had a fever, sore throat, and bleeding in her gums. Id. at 8. On September 12, 2007, Ms. Harris returned with Bre for a follow up with Dr. Vanderburg. Dr. Vanderburg treated Bre with an antibiotic administered by intramuscular injection and recommended a follow up appointment in three months. Id. at 8-9.

On September 16, 2007, shortly after 11:00 P.M., Ms. Harris brought Bre to Arkansas Children's Hospital because she had fever, vomiting and dehydration. Exhibit 3 at 44. Ms. Harris also reported that she had lost weight. Id. at 57. Bre remained in the hospital until September 21, 2009, during which time many doctors examined her and conducted many tests. At discharge, the doctors listed several problems including "recurring fever, fatigue, anorexia, dehydration, macular rash, conjunctiva injection." Id. at 142.

On September 28, 2007, Ms. Harris took Bre to Le Bonheur Children's Medical Center, where she remained until October 5, 2007. Exhibit 132. For purposes of this case, the most significant event was a rheumatology evaluation by

Dr. Monica Brown and Dr. Linda K. Meyers. They suggested that Bre may have lupus and ordered tests informative for lupus. Id. at 343-45.

These tests did in fact confirm lupus. The doctors testifying also agreed with the diagnosis of lupus, see Tr. 17 (Dr. Shoenfeld), 565 (Dr. Rose). Thus, an extensive recitation of the signs and symptoms that Bre experienced is not needed.

So, too, a discourse about Bre's multi-year history of lupus is also not needed to address the issue in this case, which is whether the HPV vaccine caused Bre to suffer lupus. For purposes of making this finding, it is sufficient to note that Bre's course of lupus has been extremely severe. Sadly, Bre has suffered from many lupus complications, including damage to her kidneys and brain. Exhibit 4 at 84-87; see also Pet'r's Prehr'g Br., filed Sept. 25, 2012, at 7-8 (summarizing Bre's medical history after 2007), Resp't's Rep't, filed Jan. 27, 2012, at 3 (stating "[t]he subsequent clinical course of [Bre]'s SLE has been quite severe, and central nervous system involvement has been a major component of [Bre]'s disease" and citing records).

While Bre's ultimate diagnosis of lupus is not disputed, determining the onset of lupus is generally not straightforward. See Tr. 17, 556, 930-34, 1109-12. For background, a general discussion of the symptoms, diagnosis, and incidence of lupus is included below.

III. Lupus

Lupus is an autoimmune disease. In autoimmune diseases, "the immune system is reacting aberrantly in a very strong way against our own constituents." Tr. 27. In lupus, many organs, including skin, joints, lungs, heart, central nervous system, and hematologic system, may be affected. Tr. 551; accord Tr. 554-55. Hence, it is classified as a "systemic" disease. Tr. 16-17. In Dr. Rose's view, lupus may be "the most complex" autoimmune disease that he treats. Tr. 557.

Such complexity derives, in part, from the presentation. Lupus can appear in a variety of ways. Tr. 223-24. Dr. Shoenfeld stated: "Every lupus differs from the other. I have not seen two patients with lupus [who] are identical to each other… This is one of the most diverse diseases, and therefore, it was named the disease of 1,000 faces." Tr. 194.

The first sign or symptom of lupus "depends on who is asking and who is looking." Tr. 562 (Dr. Rose); accord Tr. 195-96 (Dr. Shoenfeld: "at the first presentation [diagnosis] will be difficult"). The initial symptom is often an

"unspecific inflammation," which may be manifest as "low-grade fever, weight loss, aches and pains, sometimes nephropathy, sometimes sore throats and rashes of all sorts." Tr. 562. According to Dr. Rose, "it has been said that almost any skin rash can be seen in lupus, from the typical one described in the criteria, also known as the butterfly rash, to all sorts of macular, circular, purpuric, [and] necrotic rashes." Tr. 554.

Researchers have identified 11 criteria for classifying lupus. Although some physicians require a patient to satisfy at least four of the criteria to diagnose lupus, Dr. Rose does not. Tr. 563-64, 1109-12. Sometimes, lupus can be diagnosed based upon fewer than four criteria, especially when the sign or symptom is closely associated with lupus. In the absence of a particular sign or symptom associated with lupus, determining when the person first began suffering from the disease is challenging. See Tr. 930-34 (Dr. Shoenfeld), 1109-12 (Dr. Rose).

The incidence of lupus varies. In the United States, there are 8-10 cases per 100,000. Tr. 917. But, in the African-American female population, the incidence is one case per 700 African-American females. Tr. 651. The incidence of lupus in identical (monozygotic) twins is higher than the incidence in fraternal twins. Tr. 919. The concordance rate means that genetics contributes to the cause of lupus. Tr. 192, 552, 652, 918-19.

Although genes are involved in developing lupus, lupus is not inherited by the simple rules of Mendelian genetics. For most cases of lupus, a single gene does not determine that the person will developed lupus. Tr. 193 (Dr. Shoenfeld: the genetics "is not one to one"), 919-20.[4] Dr. Shoenfeld stated that researchers have "found so far 33 different genes which make you more prone" to develop lupus. Tr. 920. In Dr. Rose's view, at least four genetic mutations may need to occur in combination for a person to develop lupus. Tr. 552-53. Because genetic mutations do not account for all cases of lupus, environmental factors may also contribute to its development. Tr. 192, 558-60, 652.

What environmental factors cause lupus is not established. Dr. Rose stated "the bottom line is that we don't know what causes lupus to start with." Tr. 558. Exposure to the sun may increase the likelihood of developing lupus. Tr. 190-91. Dr. Shoenfeld stated that infections may lead to the onset of autoimmune diseases

[4] Dr. Rose mentioned that a mutation in a particular gene, known as the C1q gene, causes a deficiency that develops into lupus. This particular form of lupus is almost entirely genetic. Tr. 553.

generally. See Tr. 49, 85, 90-97, 119-20, 140-41, 156, 188-91, 474-75, 480-81. The Epstein-Barr virus has particularly been associated with the development of lupus. Tr. 90, 141, 560, 638, 654-55, 673-79, 921-22.

On the other hand, the human papillomavirus has not been associated with autoimmune diseases. A potential effect of an infection with human papillomavirus is cervical cancer, but not lupus. Tr. 141.

Ms. Harris claims that the vaccine against the human papillomavirus caused her daughter to suffer lupus. The events associated with the prosecution of this claim are set forth in the next section.

IV. Procedural History

Ms. Harris filed her petition on May 26, 2010. She submitted Bre's medical records on June 11, 2010 (exhibits 1-14) and a set of affidavits (exhibits 15-22) on August 12 and 13, 2010. More medical records were filed on September 13, 2010 (exhibits 23-28). None of this material contained a report from an expert supporting Ms. Harris's claim that the HPV vaccine caused Bre's lupus.

The presiding special master granted a series of motions seeking additional time to file an expert report, totaling approximately one year. On September 11, 2011, Ms. Harris presented the report of Dr. Shoenfeld, exhibit 32.

Dr. Shoenfeld's report began with a recitation of his background in immunology and a review of Bre's medical history. Exhibit 32 at 1-2. He indicated that the aluminum adjuvant can cause lupus, and that the aluminum adjuvant in the HPV vaccine caused Bre's lupus. Id. at 5-6. Dr. Shoenfeld's report cited 85 articles (exhibits 33-117) in support of his conclusions, although some were duplicates. The presiding special master ordered that Ms. Harris file the articles that Dr. Shoenfeld cited and identify the relevant portions of the article with highlighting. Order, filed Nov. 1, 2011.

The Secretary responded to this material on January 27, 2012. The Secretary maintained that the record, including Dr. Shoenfeld's report, did not establish that Ms. Harris was entitled to compensation. Resp't's Rep't at 6.

In response to Dr. Shoenfeld's opinion, the Secretary presented the reports from Dr. Rose and Dr. Frenkel. Although Dr. Rose agreed that Bre suffered from lupus, he suggested that she may have developed lupus before she received the HPV vaccine. Exhibit A at 3-4.

Dr. Rose more broadly argued that the evidence does not support a finding that the HPV vaccine can cause lupus. Dr. Rose relied upon a study by Thomas Verstraeten, which a manufacturer of an HPV vaccine sponsored. Exhibit M (Thomas Verstraeten et al., Analysis of adverse events of potential autoimmune aetiology in a large integrated safety database of AS04 adjuvanted vaccines, 26 Vaccine 6630 (2008)).[5] The Verstraeten study integrated an analysis of many smaller studies, totaling over 68,000 participants. The authors did not find that the incidence of lupus increased among people who received an HPV vaccine. Id. Dr. Rose stated that: "The epidemiological data offered is overwhelmingly against a relationship with SLE." Exhibit A at 16.

Dr. Rose also reviewed each of the 85 articles Dr. Shoenfeld cited. Dr. Rose maintained that the cited articles did not support a causal relationship between the HPV vaccine and lupus. He wrote:

> The overwhelming majority of them were editorials and opinion papers most of them written by Dr. Shoenfeld[;] as such the arguments and ideas tended to overlap and are mostly redundant. Without exception all the reports that involve some level of systematic approach showed negative results for vaccines in relationship to SLE.

Id. at 16.

The second report filed by the Secretary came from Dr. Frenkel, who specializes in pediatric infectious diseases and immunology. Like Dr. Rose, Dr. Frenkel raised the possibility that Bre was suffering from undiagnosed lupus before she was vaccinated. Exhibit C at 3. Dr. Frenkel's report further discussed ongoing work being done to monitor HPV vaccine safety including a study by Chun Chao et al. that "failed to verify a causal relationship between HPV vaccine and autoimmune disease including SLE." Id. (citing exhibit F (Chun Chao et al., Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine, 271(2) J. Internal Medicine 193 (2012)). With regard to Dr. Shoenfeld's theory that vaccine adjuvants can cause lupus, Dr. Frenkel stated Dr. Shoenfeld "fails to offer any specifics regarding the basis of his causation opinion. He also fails to provide any relevant and reliable peer-reviewed references in support of his opinion regarding the specific role of the adjuvants in this case." Id. at 4.

[5] A duplicate of the Verstraeten study appears as exhibit 146.

The presiding special master ordered a response from Dr. Shoenfeld and repeated the requirement that Ms. Harris highlight the pertinent portions of the medical literature. Order, filed Feb. 1, 2012. On March 12, 2012, Ms. Harris filed two reports from Dr. Shoenfeld. The first, exhibit 118, responded to Dr. Rose's report. The second, exhibit 119, addressed the opinions of Dr. Frenkel. Dr. Shoenfeld cited a total of 13 (non-duplicate) articles (exhibits 121-32).

In these reports, Dr. Shoenfeld introduced a new syndrome that Dr. Shoenfeld's colleagues and he had recently "crystallized" --- the autoimmune syndrome induced by adjuvant ("ASIA"). Proponents of this syndrome maintain that an adverse effect of one type of vaccine, such as the hepatitis B vaccine, usually portends the adverse effect of another type of vaccine, such as the HPV vaccine, because the vaccines share a common denominator, the adjuvant. Exhibit 118 at 1. Dr. Shoenfeld noted that a special issue of the journal Lupus was devoted to ASIA and he cited the articles contained in that issue.

Dr. Shoenfeld responded to Dr. Frenkel's citation to the Chao article by saying that "each one of the authors was a private consultant to Merck & Co.," which manufactured the vaccine. Exhibit 118 at 2. He also stated that the editor of the Journal of the American Medical Association criticized the way that "the Gardasil vaccine was 'pushed' to the market." Id.

Dr. Shoenfeld incorporated these comments into his separate response to Dr. Frenkel. Here, Dr. Shoenfeld stated that the rash that Bre experienced before the HPV vaccination "was non-specific," in contrast to the "specific, identifiable rashes" that are associated with lupus. Exhibit 119.

The presiding special master ordered that Ms. Harris provide a list of causation theories advanced by Dr. Shoenfeld. Order, filed Mar. 20, 2012. Another order, filed April 4, 2012, scheduled a hearing for October 16, 2012.

Ms. Harris filed another report from Dr. Shoenfeld as exhibit 133 on May 7, 2012. In response to the March 20, 2012 order, Dr. Shoenfeld identified three theories: (1) adjuvant-induced autoimmunity, (2) molecular mimicry, and (3) bystander activation. Dr. Shoenfeld again cited various medical articles to support these three theories.

On May 7, 2012, the case was reassigned to the undersigned. A status conference was held on May 23, 2012, to discuss the plan to have a hearing on October 16, 2012.

The Secretary stated that she intended to respond to the recent opinions offered by Dr. Shoenfeld. She also planned to retain additional experts to address the theory based on adjuvants. The ensuing order permitted the Secretary to submit these reports by July 30, 2012. A subsequent order extended the duration of the hearing from one day (October 16, 2012) to three days (October 15-17, 2012).

After receiving an enlargement of time, the Secretary presented reports from two more experts. One of the reports was written by Theodore C. Eickhoff, a specialist in adult infectious diseases and epidemiology with experience in studying vaccines. Dr. Eickhoff described the process "by which the adverse events caused by vaccines are actually attributed to a specific vaccine." Exhibit N at 4. He cited three studies (one by Chao, the second by Slade, and the third by Mok). Id. at 4-5. Dr. Eickhoff interpreted "these epidemiological studies [as] provid[ing] no basis to believe, as Dr. Shoenfeld has suggested, that HPV vaccine has in any way caused or facilitated the development of SLE." Id. at 5.

The Secretary's last report came from Edward Cetaruk, a medical toxicologist. He "applied the principles of both experimental and clinical toxicology in conjunction with scientifically sound causation analysis methodology" to investigate "aluminum and aluminum-containing adjuvants and their potential health effects on humans." Exhibit P at 4. Dr. Cetaruk's ultimate conclusion was that "Dr. Shoenfeld fails to present a scientifically sound (i.e. supported by the medical literature – including those publications he cites in his report) case for either a general or specific causal relationship between Gardasil or its aluminum adjuvant and the development of SLE." Id. at 9.

On September 25 and 27, 2012, the parties filed additional materials before the hearing. Each party filed a brief. Both parties filed more medical articles. An extensive and digitally recorded pre-trial conference was held on October 2, 2012.

The hearing was held, as scheduled, for three days, starting on October 15, 2012, in Washington, DC. The five doctors who had submitted reports testified.

Following the hearing, the parties opted to file briefs. Ms. Harris has filed the final brief, making the case ready for adjudication.

V. Standard for Adjudication

With respect to her burden of proof, Ms. Harris argues for a standard that is less than a preponderance of the evidence. She stated "medical and scientific

certainty is not required for causation to be found pursuant to the Vaccine Act…. Rather, all that is required is a plausible theory of causation consistent with current body of scientific and medical knowledge that exists today." Pet'r's Posthr'g Br. at 7 (citing Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005)). Consistent with this view, Ms. Harris frequently solicited testimony about whether particular medical theories were "plausible." Tr. 21-22, 51, 65, 94-95, 130, 220-21, 625, 633-34, 636-39, 684-85, 690-93, 712, 1083-84, 1086-88, 1094-95.

Ms. Harris's argument does not accord with controlling precedent. The Federal Circuit has consistently rejected attempts to set petitioners' burden of proof at the plausibility level. "[P]roof of a 'plausible' or 'possible' causal link between the vaccine and the injury… is not the statutory standard." Moberly v. Sec'y of Health & Human Servs., 592 F.3d 1315, 1322 (Fed. Cir. 2010). A "petitioner must do more than demonstrate a 'plausible' or 'possible' causal link between the vaccination and the injury; he must prove his case by preponderance of the evidence." W.C. v. Sec'y of Health & Human Servs., 704 F.3d 1352, 1356 (Fed. Cir. 2013) (citing Moberly, 592 F.3d at 1322).

Consequently, the evidence in this case will be examined to determine whether Ms. Harris has established the elements of her case on a more likely than not basis. The elements of Ms. Harris's case are set forth in the often cited passage from Althen: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." Althen, 418 F.3d at 1278.

VI. *Althen* Prong One – A Medical Theory

The first prong of the Althen analysis has been described as a "can it?" question which asks whether the vaccine could cause the alleged injury. See Pafford v. Sec'y of Health & Human Servs., 451 F.3d 1352, 1356 (Fed. Cir. 2006) (affirming special master's use of "can cause" and "did cause" as consistent with the Althen test); Veryzer v. Sec'y of Health & Human Servs., 100 Fed. Cl. 344, 352 (2011) (describing the first prong of Althen as presenting the question of general causation). The Federal Circuit has characterized this aspect as "a frequently more difficult" inquiry compared to the sometimes more straightforward question of whether a petitioner suffered from a particular disease. Hibbard v. Sec'y of Health and Human Servs., 698 F.3d 1355, 1365 (Fed. Cir. 2012).

An important aspect to evaluating whether petitioners have established the persuasiveness of a theory proposed by their expert is to consider what information is relevant to assessing the reliability of a theory. As discussed in section VI.A, there is a consensus that some types of studies provide more meaningful information than other types of studies.

In trying to determine whether there is a reliable basis for a petitioner's theory that a vaccine can cause a particular disease (the first prong of Althen), a potentially useful study is an epidemiological one. Here, the parties submitted four epidemiologic studies involving vaccinations against the human papillomavirus. These are discussed in section B. They are discussed before a more in-depth evaluation of Dr. Shoenfeld's theories because the epidemiological studies provide some information about the reliability of all Dr. Shoenfeld's theories. Because epidemiological studies cannot definitively resolve whether an HPV vaccine can cause lupus, Dr. Shoenfeld's theories are separately addressed in section C.

A. Value of Scientific Studies

While opining on whether an HPV vaccine can cause lupus, the parties' experts have cited various scientific studies. A discussion of the expert opinions about a selection of the cited scientific studies appears below. The experts' opinions differed at several points, offering conflicting interpretations on the value and relevance of the studies discussed. When the evidence is in conflict, the special master may determine what evidence is more persuasive. Broekelschen v. Sec'y of Health & Human Servs., 618 F.3d 1339, 1346-49 (Fed. Cir. 2010); see also Whitecotton v. Sec'y of Health & Human Servs., 81 F.3d 1099, 1108 (Fed. Cir. 1996).

The expert witnesses explained the process that doctors use in reaching conclusions about causation. There was general agreement that the first step is an observation that two events occur in sequence. See Tr. 26, 509, 593. As Dr. Shoenfeld stated: "[E]very disease, like Mao Tse-Tung says, every long march start[s] with one step[;] every new syndrome start[s] with [a] case report." Tr. 197. The Secretary's experts emphasized that case reports usually do not contain sufficient evidence to establish causation. Tr. 509-10 (Dr. Eickhoff), 579-80 (Dr. Rose), 1087-88 (Dr. Cetaruk).[6] After several separately presented case reports,

[6] The opinions from the government's experts about the relative usefulness of different types of evidence that might support an opinion regarding causation is quite similar to a view expressed in a publication from the Federal Judicial Center. The Federal Judicial Center has (continued…)

they might be collected into a "case series." Tr. 197-98 (Dr. Shoenfeld). A case series, like a case report, "cannot in and of itself show a causal effect." Tr. 510 (Dr. Eickhoff).

These groups of observations "might lead to other studies that will prove a [causal] relationship." Tr. 1087. Examples of these other more probative studies include experimental animal models and reports of rechallenge. Tr. 69, 132, 408-10 (Dr. Shoenfeld). To Dr. Shoenfeld, "the experimental models are much more scientifically [informative], scientific as in evidence, than just the case report." Tr. 197.

Another potentially useful type of study is an epidemiological study. "Epidemiology is the study of disease or some aspect of disease in a population." Tr. 508. Epidemiology can show an increased incidence of disease in particular populations. This increased incidence, in turn, may support an inference that an exposure to a substance caused the disease. See Tr. 59, 73, 519. Epidemiological studies, however, are limited in their ability to detect increased incidences of diseases that are rare. Tr. 579-80, 1091.

B. Epidemiological Studies

In a single person, determining whether an outside factor (such as a vaccine) caused a disease (such as lupus) may be difficult. It may be that the foreign substance did cause the disease. However, it may also be true that the introduction of the outside agent did not cause the illness. In other words, the exposure to the outside agent was coincident to the onset of the disease.

Separating out these coincidences from causal events is difficult, but epidemiological studies are a useful part of the process. An advantage to epidemiological studies is that they can account for the background incidence of a disease -- the number of cases that are expected to occur in the population without any effect from the putative causative factor. Michael D. Green et al., Reference

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published a series of guides designed "to assist judges . . . in reaching an informed and reasoned assessment concerning the basis of expert evidence." Jerome P. Kassirer & Gladys Kessler, Preface, in Reference Manual on Scientific Evidence (Federal Judicial Center, 3d ed. 2011). A pertinent guide contained therein states that "Anecdotal evidence usually amounts to reports that events of one kind are followed by events of another kind. Typically, the reports are not even sufficient to show association, because there is no comparison group." David H. Kaye & David A. Freedman, Reference Guide on Statistics, in Reference Manual on Scientific Evidence 211, 218 (Federal Judicial Center, 3d ed. 2011).

Guide on Epidemiology, in Reference Manual on Scientific Evidence 549, 570 (Federal Judicial Center, 3d ed. 2011) (calculating attributable risk using epidemiological incidence data from cohort studies). The Verstraeten study commented upon how the background rate can help distinguish a coincidence from an actual increase in disease:

> Bearing in mind the background incidence of autoimmune disorders in the adolescent and young adult population, it seems likely that, with broader use of HPV vaccines or other vaccines targeting this age group, autoimmune disorders will be reported in temporal association with vaccine administration even in the absence of a causal relationship.

Exhibit M (Verstraeten) at 6633.

As a co-author, Dr. Shoenfeld has recommended additional studies of the HPV vaccine with a longer follow-up period that would take into account "the expected rate of [autoimmunity] in young girls." Exhibit 145 (Ari Balofsky et al., The new H1N1 and HPV vaccines and old fears, 22 Current Op. in Rheumatology 431 (2010)) at 433. Dr. Shoenfeld's testimony about the background rate was similar. Tr. 426-32.

Epidemiological studies can detect when the incidence of disease exceeds the background rate. For example, in the 1970s, epidemiological studies discovered an increased incidence of Guillain-Barré syndrome among people receiving the swine flu vaccine. Tr. 539-40. Dr. Shoenfeld stated that more recently, large studies demonstrated an increased number of cases of narcolepsy in Finland among people who received a type of flu vaccine. Tr. 59-60.[7]

While epidemiological studies can establish an increased incidence, and this increased incidence can support an inference of causation, epidemiological studies cannot absolutely refute a causal connection. Epidemiological studies cannot prove a negative. It is always possible that another epidemiological study involving a bigger population will detect an increased risk not otherwise apparent

[7] Although Dr. Shoenfeld testified about this study, Dr. Shoenfeld did not cite the study in his report and the petitioner did not file the relevant article. Consequently, the Secretary objected to Dr. Shoenfeld's testimony about an article not included in the record. Tr. 58-61.

in smaller studies.[8] Nevertheless, epidemiological studies have been considered relevant and meaningful evidence in determining causation. See Holmes v. Sec'y of Health & Human Servs., 115 Fed. Cl. 469, 485 (2014) ("causation can without question be based on epidemiological evidence") (citing Knudsen v. Sec'y of Health & Human Servs., 35 F.3d 543, 549 (Fed. Cir.1994)); see also Andreu v. Sec'y of Dep't of Health & Human Servs., 569 F.3d 1367, 1379 (Fed. Cir. 2009) ("the special master can consider [epidemiological evidence] in reaching an informed judgment as to whether a particular vaccination likely caused a particular injury"); Koehn v. Sec'y of Health & Human Servs., 11-355V, 2013 WL 3214877, at *20 (Fed. Cl. May 30, 2013) (discussing epidemiology articles as additional reason for finding petitioner's causation theory unlikely and citing Andreu), mot. for review denied sub nom. C.K. v. Sec'y of Health & Human Servs., 113 Fed. Cl. 757 (2013), appeal docketed, No. 14-5054 (Fed. Cir. Feb. 18, 2014).

Consideration of epidemiological studies is not unique to the Vaccine Program and courts, in the context of evaluating whether plaintiffs established an exposure caused them to suffer a personal injury, have looked at epidemiological studies. For example, when a plaintiff alleged silicone breast implants caused her to develop an autoimmune disease, she advanced reports from two doctors, attempting to establish that silicone breast implants can cause disease in people. The defendant submitted at least 17 epidemiological studies to support its argument that silicone breast implants do not cause disease. The district court excluded the plaintiff's evidence and granted summary judgment. Norris v. Baxter Healthcare Corp., 397 F.3d 878, 880-81, 887 n.5 (10th Cir. 2005). On appeal, the Tenth Circuit affirmed, holding that while "the presence of epidemiology does not necessarily end the inquiry, where epidemiology is available, it cannot be ignored. As the best evidence of general causation, it must be addressed." Id. at 882. The court clarified: "We are not holding that epidemiological studies are always necessary in a toxic tort case. We are simply holding that where there is a large body of contrary epidemiological evidence, it is necessary to at least address it with evidence that is based on medically reliable and scientifically valid methodology." Id.

[8] For example, Dr. Shoenfeld stated that a study has found an increased risk of multiple sclerosis among people who received the hepatitis B vaccine. But, this risk was not apparent until more than two years later. Tr. 115, 156, 183-86, 427-28. Again, Dr. Shoenfeld did not cite this study and it does not appear in the record.

Here, the record includes epidemiological studies by Chao, Slade, Mok, and Verstraeten. These articles and the experts' commentary on them are discussed below.

1. Chao

When the manufacturer of an HPV vaccine, Merck, was obtaining regulatory approval for Gardasil from the FDA, Merck committed to funding post-licensure studies about the safety of Gardasil. One such study was conducted by 13 employees of two large health maintenance organizations in California. Tr. 124, 526, 537-38, 544. The lead author of the ensuing article is Chun Chao, PhD.

Through computerized medical records, Chao and colleagues identified more than 180,000 women who received at least one dose of the HPV vaccine. The researchers followed these women for 180 days, looking to see if they developed any autoimmune diseases. Lupus was one of the autoimmune diseases for which the researchers searched. Exhibit F (Chao) at 193-94; see also Tr. 438, 512-13, 520-21.

The incidence of lupus among women who received the HPV vaccine was not statistically increased compared to women who did not receive the HPV vaccine. Exhibit F (Chao) at 199 (table 3); see also Tr. 523-24, 543. Dr. Frenkel interpreted this finding as "fail[ing] to verify a causal relationship between HPV vaccine and autoimmune disease including SLE." Exhibit C at 3. Dr. Eickhoff opined that this study showed the HPV vaccine "did not result in an increased incidence of lupus." Tr. 524.

Dr. Shoenfeld rejected the data Chao presented. He stated flatly that "this is a fraud in medicine." Tr. 438; accord Tr. 423. In his testimony, Dr. Shoenfeld proposed that the payments from Merck influenced the outcome of the study. He went so far as to say that Merck employees may have ghostwritten the article. Dr. Shoenfeld acknowledged that he did not have any direct knowledge about Dr. Chao or ghostwriting. Tr. 423, 436-39, 491-96. Dr. Shoenfeld made a similar, although less bombastic, criticism in a letter addressed to the editors of the journal that published the Chao article. Exhibit 126.[9]

[9] Exhibit 126 is the manuscript version of Dr. Shoenfeld's letter. The published version appears in 272 J. Internal Medicine 98 (2012).

In her reply brief, Ms. Harris repeats Dr. Shoenfeld's accusation. She thus argues "the Chao study is tainted because it was funded by Merck." Pet'r's Posthr'g Reply, filed Aug. 26, 2013, at 13 (citing Exxon Shipping Co. v. Baker, 554 U.S. 471, 501 n.17 (2008); UFCW Local 1776 v. Eli Lilly and Co. (In re Zyprexa Prods. Liab. Litig.), 253 F.R.D. 69, 107 (E.D.N.Y. 2008), rev'd on other grounds, 620 F.3d 121 (2d Cir. 2010)), Ms. Harris contends that "given that funding bias is a true concept,… [t]he reliability of the results of the Chao study must be questioned." Pet'r's Posthr'g Reply, filed Aug. 26, 2013, at 14.[10]

2. Slade

Another post-licensure study of the safety of Gardasil was led by Barbara Slade. The funding for this study came from the Centers for Disease Control and Prevention and the Food and Drug Administration. An external source did not sponsor this investigation. Exhibit K (Slade) at 757.

Dr. Slade and her team searched for health problems reported to the Vaccine Adverse Event Reporting System (VAERS). They determined the frequency of reports of different health problems per 100,000 doses of vaccine distributed. The researchers compared reporting rates for Gardasil and reporting rates for other vaccines. Exhibit K at 750-51; see also Tr. 441, 511-15. The authors grouped the adverse events following immunizations into 15 categories, including dizziness, hypersensitivity reaction, Guillain-Barré syndrome, death, and autoimmune disorder. Exhibit K at 753 (table 2). The group of autoimmune disorders included 18 reports of lupus. Exhibit K at 755.

Dr. Slade and colleagues identified an increased reporting ratio for syncope and venous thromboembolic events. They did not otherwise detect an increased rate of reports for any of the other conditions. Exhibit K at 755; Tr. 516-17.[11]

Dr. Shoenfeld questioned the methodology Dr. Slade used. In his opinion, the different diseases listed in table 2 should not have been analyzed separately. Dr. Shoenfeld stated that the reports of Guillain-Barré syndrome, the reports of thromboembolic phenomena, and the reports of transverse myelitis should have

[10] Because it was evident that the Secretary intended to rely upon the Chao study, the better practice would have been for Ms. Harris to present these cases in her initial posthearing brief.

[11] Dr. Slade and colleagues noted some of the limitations of their analysis, including problems associated with the underlying VAERS reports. Exhibit K (Slade) at 756-57.

been grouped into one large category. Tr. 212-13. This approach is consistent with Dr. Shoenfeld's overall view that all autoimmune diseases are the same. Dr. Shoenfeld asserted that "if we will combine[] [the reports from all categories] and I will use the proper statistical analysis, I will find that it is statistically significant." Tr. 213. Dr. Shoenfeld did not actually perform this analysis, but he averred, "I can assure you that as somebody can find that it's not [statistically significant], I can find that it is." Tr. 929.

3. Mok

A third epidemiological study involving Gardasil was conducted by researchers from Hong Kong. Merck funded the study and provided some assistance. However, the primary investigator retained independence and did not have any financial interest in Merck. Exhibit R (Chi Chiu Mok et al., Immunogenicity and safety of a quadrivalent human papillomavirus vaccine in patients with systemic lupus erythematosus: a case-control study, Annals of the Rheumatic Diseases (electronically published May 15, 2012)) at 6.

Dr. Mok and colleagues investigated Gardasil's safety by giving the vaccine to 50 women who suffered from stable lupus. They identified the number of flares in these women and compared the number of flares to a control group of 50 women with lupus who did not receive Gardasil. Exhibit R (Mok) at 1; Tr. 513-14, 528-31.

The incidence of lupus worsening were similar. Exhibit R at 3; Tr. 530. Dr. Eickhoff described this study as "reassuring," although it was "small." Tr. 531, 537.

Dr. Shoenfeld questioned the usefulness of this study. He asserted that all the subjects in this experiment had a suppressed immune system from receiving medication for their lupus. This suppressed immune system mitigated the effect of the vaccine including any harmful consequences. Tr. 445-50, 940-44. Dr. Rose countered that whether an anti-inflammatory medication would prevent recipients of a vaccine from flaring is "an extremely complicated matter." Tr. 659.

4. Verstraeten

Researchers at GlaxoSmithKline Biologics ("GSK"), led by Thomas Verstraeten, conducted an integrated analysis of data from over 68,000 participants in GSK-funded vaccine trials. Exhibit M (Verstraeten) at 6630. The objective of the GSK analysis was to assess the occurrence of autoimmune-type adverse events

following aluminum-adjuvanted vaccination. Id. at 6631. The analysis included GSK trials of AS04 adjuvanted HPV-16/18 (Ceravix), HSV and HBV (Fendrix) vaccines. Id. The adjuvant AS04 is a combination of aluminum salt with a lipopolysaccharide derivative called "MPL." Id.

Verstraeten et al. found no increased risk of autoimmune disorders associated with the aluminum-adjuvanted vaccines. Id. at 6637 ("results… do not suggest any causal association between AS04 adjuvanted vaccines and development of autoimmune disorders"). Dr. Rose referred to the Verstraeten findings as an "encouraging" indication that future epidemiologic evidence associating the HPV vaccine with lupus should not be anticipated. Exhibit A at 3-4.

Dr. Shoenfeld interpreted the Verstraeten article very differently, relying on it as evidence of hyperstimulation of the immune system following vaccination. Tr. 75-76, 926-927. Dr. Shoenfeld emphasized the objective of the paper -- assessing the risks of adjuvanted vaccines -- rather than the findings. While Verstraeten et al. provide a background of the immune-stimulating role of adjuvants in vaccines, they found no increased incidence of lupus following vaccination with an aluminum-adjuvanted HPV vaccine. Exhibit M (Verstraeten) at 6631-34.

5. Conclusion regarding Epidemiological Studies

Collectively, these epidemiological studies weigh against finding that an HPV vaccine contributes to an increased risk of lupus. Each of these studies has some strength and some weaknesses. For example, the source for Dr. Chao's funding opens a potential (if ultimately unresolvable) argument that her conclusions are not valid. But, funding as a potential source of bias or interest in outcome is not an issue for Dr. Slade. Similarly, some studies have many thousands of participants, but the Mok study involved fewer than 100. In short, none of the epidemiological studies are perfect. But, a perfect scientific study is not required by the relevant legal standards applying to Ms. Harris's claim.

The overall effect of the epidemiological studies casts some doubt about the persuasiveness and plausibility of Dr. Shoenfeld's theories. If it were likely that the HPV vaccine were causing lupus (regardless of the precise mechanism), then there should be some evidence of an increased incidence of lupus. The studies have not detected an increased incidence.

Even a very large epidemiological study cannot rule out conclusively the possibility that the vaccine may cause lupus. Thus, the following section discusses whether any of Dr. Shoenfeld's theories proposing to explain a causal connection between vaccination and lupus are persuasive. See Holmes, 115 Fed.Cl. at 486 ("Absent epidemiological evidence to support causation, it remained the job of petitioner, not respondent, to supply a reputable medical or scientific explanation of causation.").

C. Dr. Shoenfeld's Theories

Dr. Shoenfeld holds the broad opinion that "any vaccine can cause any autoimmune disease at any time." Tr. 406. As to the specific method for how a vaccine can cause an autoimmune disease, Dr. Shoenfeld presented three theories in a supplemental report that he prepared in response to an order. Exhibit 133. The three theories are: (1) adjuvant-induced autoimmunity, (2) molecular mimicry, and (3) bystander activation. Dr. Shoenfeld ranked the adjuvant theory as "the most important." Molecular mimicry was next, followed by bystander activation. Tr. 156; see also Tr. 964 (indicating that the adjuvant part of a vaccine is probably stronger than the viral part of a vaccine). These theories will be evaluated in the sequence that Dr. Shoenfeld listed them, beginning with the most important, the adjuvant theory.

1. Adjuvant

Adjuvants are substances that "enhance the immune system." Tr. 38. They are often incorporated into a vaccine because the vaccine contains a less potent form of the substance (bacterium or virus) that causes the infection naturally. Tr. 37-38, 989-90.

Different compounds act as adjuvants. Common examples include aluminum, pristane, squalene, and Freund's adjuvant. Scientists have not determined how any adjuvant stimulates the immune system, although they have proposed various hypotheses. Tr. 38-41.

Dr. Shoenfeld has advanced the theory that the adjuvant in the HPV vaccine can cause lupus. An important aspect of Dr. Shoenfeld's theory is that he considers all adjuvants to be the same. All adjuvants cause stimulation of the immune system normally and in Dr. Shoenfeld's theory the adjuvant causes an

abnormally hyperstimulated immune system. Tr. 167-68, 172-73; see also Tr. 669-70 (Dr. Frenkel's explanation of hyperstimulation).[12]

The Secretary's experts disagreed with Dr. Shoenfeld's assertion that all adjuvants are the same. Tr. 687 (Dr. Rose: it is "crucially important to note that [pristane and aluminum are] very different adjuvants and it is likely that they worked in different fashions and that they have different immunologic consequences"), 735-36 (Dr. Frenkel: "I think there's animal data that suggests that pristane can cause autoimmune phenomenon. I don't think there's animal data that is convincing… that aluminum can cause autoimmune phenomenon."), 1001-02 (Dr. Cetaruk interpreting exhibit Y: "different adjuvants will elicit different responses and, for that matter, a given adjuvant might elicit a different response at a different dose."). On this point, the Government's experts were more persuasive partly because the literature supported their view. A prominent support for treating different adjuvants differently was the article by Michael Potter and Judith S. Wax. Exhibit Y (Michael Potter & Judith S. Wax, Peritoneal Plasmacytomagenesis in Mice: Comparison of Different Pristane Dose Regimens, 71(2) J. Nat'l Cancer Inst. 391 (1983)). This study showed that different adjuvants (and the same adjuvant in different doses) caused different immunological effects. Id.; Tr. 1001-02. Dr. Shoenfeld, on the other hand, did not present any persuasive reason for treating aluminum the same as pristane.

Because preponderant evidence suggests that pristane may stimulate the immune system in a way that aluminum does not, Dr. Shoenfeld's extensive discussion of studies involving pristane is not relevant. Thus, the Wesley Reeves studies (Tr. 486) are not discussed, although they were considered. Instead of analyzing evidence involving an adjuvant that Bre did not receive, it is more useful to focus on the adjuvant present in the HPV vaccine that Bre received, aluminum.

Bre's exposures to aluminum through the two doses of the HPV vaccine were not her only exposures to aluminum. Aluminum is present in most drinking water and in many foods. Tr. 180. Dr. Cetaruk, the toxicologist, explained that the method of exposure (for example, ingestion or intramuscular injection) affects how much of the substance remains available to the body. Tr. 1104-08. In the normal course of digestion, the body largely eliminates aluminum. Tr. 1107.

[12] Dr. Shoenfeld's presentation emphasized the effect of the adjuvant on the immune system. However, he did also mention that the adjuvant could also have a toxic effect. Tr. 175-76.

Additionally, there is some evidence that the body also eliminates aluminum that is injected as part of a vaccine. "Preliminary animal experiments have shown that the aluminum adjuvants are dissolved by citrate in the interstitial fluid, leaving the body rapidly. The ability of the body to eliminate aluminum-containing adjuvants may be partly responsible for the excellent safety record of these adjuvants." Exhibit BB (Thomas C. Eickhoff & Martin Myers, Workshop summary: aluminum in vaccines, 20 Vaccine S1 (2002)) at S2.[13]

Considering if aluminum could cause lupus initially raises the question of whether the persistence of aluminum in the body could explain why lupus is a chronic disease. See Tr. 956-57. Dr. Shoenfeld did not state whether he expected aluminum would persist in the body long enough to cause a chronic disease like lupus. However, Dr. Shoenfeld also answered "absolutely" to the question "if the aluminum is excreted from the body quickly[,] it still can cause lupus?" Tr. 957.

To support the proposition that aluminum from a vaccine may remain in the body, Dr. Shoenfeld cited the work led by Romain Gherardi. Tr. 69-72, 173-74, 957-59. Dr. Gherardi's work was one of two sets of studies investigating aluminum's effect on living beings. Dr. Gherardi showed that aluminum may remain at the site of an injected vaccine for years. Exhibit 137 (Romain K. Gherardi & François-Jérôme Authier, Aluminum inclusion macrophagic myofasciitis: a recently identified condition, 23(4) Immunology Allergy Clinics N. Am. 699 (2003)) at 703. Many people suffered from chronic fatigue as well as muscle pain, and Dr. Gherardi coined the phrase macrophagic myofasciitis, frequently abbreviated as MMF, to describe this condition.[14] Id. at 702-03.

The World Health Organization ("WHO") acted in response to Dr. Gherardi's findings. The WHO investigated whether people whose vaccination sites contained a persistent amount of aluminum suffered any multi-system disorder. The WHO concluded that "MMF represent[s] a simple marker of vaccination with long-term persistence of aluminum at the injection site and local inflammatory response to it, without other symptoms or consequences." Exhibit Z

[13] At first, Dr. Shoenfeld agreed with this assessment. But, he also added that the reference to S in the pagination meant that this article came from a supplemental issue of the journal and supplements are not peer-reviewed. Tr. 462-65.

[14] Although Dr. Gherardi uses the term MMF to describe a group of symptoms, others have associated the term with the histologic lesion described by Dr. Gherardi in 1998. Exhibit BB (Eickhoff) at S3.

(Statement from the Global Advisory Committee on Vaccine Safety on aluminum-containing vaccines, World Health Organization (last reviewed Dec. 3, 2008)); see also exhibit BB (Eickhoff) at S4 ("Causality has not been established for Dr. Gherardi's claim that MMF, the histologic entity, is associated with a 'symptom complex' of fatigue and ascending myalgias"); but see Tr. 462-65 (Dr. Shoenfeld: "Supplements are not peer reviewed."). The WHO reached this conclusion based on, among other work, an experiment that scientists from Aventis Pasteur performed on monkeys. This study found that monkeys who received an injection of aluminum, which persisted at the injection site, did not have any abnormal clinical signs. See exhibit CC (François Verdier et al., Aluminum assay and evaluation of the local reaction at several time points after intramuscular administration of aluminum containing vaccines in the Cynomolgus monkey, 23 Vaccine 1359 (2005)); see also Tr. 1021-23.

Another set of studies involving aluminum and living beings was conducted by a group of researchers led by Dr. Christopher Shaw. Dr. Shaw explored whether vaccines given to military personnel contributed to their development of Gulf War syndrome. Tr. 1036-37; see also Tr. 73-75. Dr. Shaw and colleagues gave mice the amount of aluminum equivalent to the amount of aluminum contained in the anthrax vaccine. These mice displayed some cognitive problems and were found to have fewer neurons in their spinal cord. Exhibit 143 (Michael S. Petrik et al., Aluminum Adjuvant Linked to Gulf War Illness Induces Motor Neuron Death in Mice, 9 NeuroMolecular Med. 83 (2007)); Tr. 1039-42.

Dr. Shoenfeld interpreted the Petrik study as showing "an adjuvant [can] cause a strenuous effect on different systems in our body, and specifically, the immune system." Tr. 75. In Dr. Shoenfeld's opinion, the mice's "cognitive impairment is [evidence of] autoimmunity and it is believed that the deaths of the neurons is also autoimmune in nature." Tr. 172. However, Dr. Cetaruk asserted that the only immunologic test on these mice showed an increased number of antibodies to squalene. Tr. 1039. Consequently, Dr. Cetaruk stated that the Petrik study was useful for looking at motor neuron diseases, such as amyotrophic lateral sclerosis, and cognitive diseases only. Tr. 1043.

Without citing any specific articles, some experts discussed how an unusually high exposure to aluminum affects people. For example, years ago, the dialysis solution used for people with impaired kidneys contained aluminum creating an exposure to aluminum. Dr. Cetaruk said that dialysis patients receiving this formulation of solution often accumulated aluminum in their kidneys as they are unable to excrete it normally. Tr. 1011, 1025, 1078. In addition, welders have

higher than normal exposure to aluminum. Tr. 1101. Dr. Cetaruk asserted that neither group had an increased incidence of lupus. Tr. 1101-02.

In sum, Ms. Harris has not established the persuasiveness of Dr. Shoenfeld's theory that the aluminum adjuvant in the HPV vaccine can cause lupus. The evidence surrounding this theory suggests that the theory is not reliable. In the mice model involving aluminum from Dr. Petrik's group, the mice exposed to aluminum developed some cognitive impairment and, more drastically, lost neurons in their spinal cord. These symptoms are not characteristic of lupus, even though cases of lupus may involve cognitive problems. The monkeys in Dr. Verdier's experiment did not development any systemic disease after they were injected with aluminum. Similarly, the people with MMF were not reported to have developed any autoimmune disease like lupus. Finally, the anecdotal information about dialysis patients and welders was that they, too, did not develop lupus. In short, while a dose of aluminum in an amount exceeding the normal exposure could, as a purely theoretical matter, cause some disease, there is no persuasive evidence that an aluminum-caused disease would look anything like lupus.

A specific finding that an aluminum adjuvant is not likely to cause lupus is in accord with the general information about aluminum adjuvants. Aluminum has been included as an adjuvant in vaccines since the 1920's. During this time, billions of doses of vaccines with aluminum adjuvants have been administered and the adjuvant in the vaccine has been considered safe. Exhibit M (Verstraeten) at 6637. Ms. Harris has not presented any persuasive evidence to create an exception for lupus.

2. Molecular Mimicry

In a single paragraph, Dr. Shoenfeld's May 6, 2012 report presented molecular mimicry as another theory to explain how the HPV vaccine can cause lupus. He stated: "an infectious antigen incorporated in vaccines . . . may resemble host antigens." Exhibit 133 at 3. The vaccinee may develop an autoimmune condition when "the autoantibodies against the infectious agent or the vaccine ingredients, 'home' to tissue antigens which have a similar (molecular mimicry) structure." Id.

In his testimony, Dr. Shoenfeld attempted to establish the foundation for this theory. He stated that the medical community understands that an infection with the streptococcus bacteria can cause rheumatic fever because the streptococcus

bacteria contain a substance, known as an M protein, that is also present in the heart. Tr. 84-86.

Dr. Shoenfeld also cited a paper in which he, as a co-author, identified how other combinations of pathogens and host antigens could cause a disease. Exhibit 138 (Miri Blank et al., Molecular Mimicry and Auto-Immunity, 32 Clinical Rev. in Allergy & Immunology 111 (2007)) at 113; Tr. 89-90.[15] The Blank authors used a computer to screen antibodies to find evidence of similarities with organs. In this paper, Dr. Shoenfeld stated "not every crossreaction or homology in amino acid sequences between a self-infecting and infecting agent has a biological function." Exhibit 138 at 112; Tr. 470. The Blank researchers did not disclose the minimum number of amino acids that is needed to establish homology but, in his testimony, Dr. Shoenfeld asserted that as few as four amino acids could be sufficient. Tr. 146.

The Secretary's experts questioned the reliability of using molecular mimicry to explain how the HPV vaccine can cause lupus. Preliminarily, Dr. Rose and Dr. Frenkel agreed that molecular mimicry was a biologically plausible explanation for why rheumatic fever sometimes follows an infection with streptococcus bacteria. Tr. 625-29, 672, 692-93. But, neither Dr. Rose nor Dr. Frenkel saw any evidence that components of the HPV vaccine shared homology with the parts of the body involved in lupus. Tr. 638 (Dr. Rose: "I did not see homology data between any of Bre's human tissue . . . with the L1 component of the vaccine"), 673 (Dr. Frenkel).

Dr. Shoenfeld agreed that homology has not been established. When asked about this topic, he stated "We don't know yet. . . . Nobody so far [has] tested for molecular mimicry except of the measles [vaccine]. . . . I believe that in the future it will be found by having what we call genomic analysis." Tr. 147. Later, Dr. Shoenfeld asserted that if his laboratory received Gardasil from the manufacturer, he could conduct the relevant study "in two weeks' time." Tr. 473.

The lack of established homology is an impediment to accepting as persuasive Dr. Shoenfeld's theory that the HPV vaccine can cause lupus via molecular mimicry. Dr. Shoenfeld's assertion of the theory, by itself, does not carry the petitioner's burden of presenting a persuasive and reliable theory. See Moberly, 592 F.3d at 1325. One criterion that a special master may use in

[15] Dr. Shoenfeld also referred to a paper by Dimitri Bogdanos. However, the Secretary objected to testimony on this paper because Dr. Shoenfeld did not cite the paper and the petitioner did not file it. Tr. 87-90.

evaluating the reliability of a theory is whether the theory can be tested and whether it has been tested. See Terran v. Sec'y of Health & Human Servs., 195 F.3d 1302, 1316 (Fed. Cir. 1999) (citing Daubert v. Merrell Dow Pharm., Inc., 509 U.S. 579 (1993)). Here, the Blank paper demonstrates that homology can be established and Dr. Shoenfeld acknowledged that his colleagues and he could perform the necessary test. However, this testing has not been done and this lack of testing for homology undercuts the persuasiveness of the theory.[16]

3. Bystander Activation

The third theory proposed in Dr. Shoenfeld's May 6, 2012 report was bystander activation. Under this theory, the exposure to an infectious antigen (or vaccine) prompts lymphocytes to go to the area of infection and inflammation develops. The inflammation, in turn, damages or destroys tissue and the damage exposes other host parts to the immune system. The immune system sends additional lymphocytes to attack the host tissue. Exhibit 133 at 4. Dr. Shoenfeld's testimony was similar. Tr. 476-81; see also Tr. 93-95, 147-51. In support of the bystander activation theory, Dr. Shoenfeld cited two articles, one published in 1989 and the other published in 1998. Exhibit 133 at 4.

Dr. Shoenfeld stated that bystander activation was his least preferred theory, falling after adjuvant induced autoimmunity and molecular mimicry. Tr. 156. In Dr. Shoenfeld's view, bystander activation was relatively weaker than the other two theories, although still biologically plausible, because there are no experimental models for bystander activation. Id. He also described bystander activation as "one of the first theories for autoimmunity." Tr. 129. But, "[t]oday, people believe more in the molecular mimicry, and the toll-like receptor activity and so forth." Id.

The Secretary's experts did not discuss bystander activation extensively. On cross-examination, Dr. Frenkel indicated that bystander activation might be a plausible explanation for some autoimmune diseases but not necessarily an

[16] Identifying some homology between the HPV vaccine and host tissue would simply be one step to establishing that the vaccine can cause a disease via molecular mimicry. Homology is a necessary step, but not a sufficient step, along this pathway because, as Dr. Shoenfeld stated, "not every . . . homology in amino acid sequences . . . has a biological function." Exhibit 138 at 112. Because there is no evidence of homology in this case, it is not necessary to resolve whether evidence of homology is a persuasive basis for inferring causation in the Vaccine Program.

explanation for lupus. Tr. 693. Dr. Rose did not see any persuasive evidence regarding bystander activation and could not say that bystander activation was a biologically plausible theory. Tr. 638-39.

Overall, the evidence surrounding bystander activation was not persuasive. The theory appears to be an older theory now supplanted by other ideas such as molecular mimicry. When Dr. Shoenfeld was asked whether he believed that bystander activation was a more-likely-than-not explanation, he responded "Absolutely no." Tr. 157.

D. Conclusion regarding *Althen* Prong One

Ms. Harris's claim that the HPV vaccine can cause lupus falls short in several respects. She has advocated that the appropriate benchmark is a plausible medical theory, but the Federal Circuit has consistently and explicitly rejected that standard. Under the statutory standard, which is preponderance of evidence, Ms. Harris's evidence is lacking.

The Secretary has introduced a strong type of evidence, epidemiological studies, that suggest the HPV vaccine is unlikely to cause lupus. Ms. Harris countered with the presentation of case reports. But, case reports are generally not a valuable form of evidence as the Federal Judicial Center has explained. Hence, although the case reports were considered, they are not discussed.

Through Dr. Shoenfeld, Ms. Harris has proposed three theories to connect the HPV vaccine to lupus. Ms. Harris has not demonstrated the persuasiveness of these theories. They are much more like untested hypotheses than valid theories to explain how HPV vaccine can cause lupus. Although additional study and testing may ultimately show that sound and reliable science underlies Dr. Shoenfeld's theories, the record in this case contains too much extrapolation and conjecture for the theories to be accepted. See La Londe v. Sec'y of Health & Human Servs., 110 Fed. Cl.184, 201 (2013) (the petitioner's expert "could not back up his hypothesis with a reliable medical or scientific explanation. . . . [The special master] quite properly required petitioner to carry her burden to bring forward a reliable medical or scientific explanation"), aff'd 746 F.3d 1334, 1340 (Fed. Cir. 2014); Langland v. Sec'y of Health & Human Servs., 109 Fed. Cl. 421, 441 (2013) ("the Special Master did not commit a legal error by requiring a sufficiently-detailed explanation of how" a vaccine can cause a disease); Taylor v. Sec'y of Health & Human Servs., 108 Fed. Cl. 807, 819 (2013) ("the mere existence" of expert testimony about a

theory "is insufficient to satisfy the burden of showing a 'persuasive' medical theory --- this theory must also preponderate").

VII. *Althen* Prong Three -- Timing

In addition to presenting a reliable medical theory explaining how the HPV vaccine can cause lupus, Ms. Harris must also show that Bre's first manifestation of lupus occurred in a medically appropriate timeframe to infer causation. Bazan v. Sec'y of Health & Human Servs., 539 F.3d 1347, 1352 (Fed. Cir. 2008). To satisfy the third Althen prong, petitioner's burden is to present "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." Bazan, 539 F.3d at 1352; accord Shapiro v. Sec'y of Health & Human Servs., 101 Fed. Cl. 532, 542-43 (2011), reconsideration denied after remand, 105 Fed. Cl. 353 (Fed. Cl. 2012), aff'd without opinion, 503 Fed. Appx. 952 (Fed. Cir. 2013).

Dr. Shoenfeld presented two ideas regarding the amount of time that is expected to pass if a vaccine caused lupus. The first concept was, to use Dr. Shoenfeld's word, the "classic" amount of time, three weeks. Tr. 26; accord Tr. 96-97. The second idea can be considered a new understanding of the temporal relationship, although Dr. Shoenfeld did not use the word "new." In Dr. Shoenfeld's view, because aluminum persists in the body, the interval between vaccination and the onset of disease can be much longer than previously expected. Tr. 152, 181-87. Dr. Shoenfeld was willing to accept a seven-year interval as plausible. Tr. 220.

Although Dr. Shoenfeld's extended latency has previously been found problematic, see Hennessey v. Sec'y of Health & Human Servs., No. 01-190, 2009 WL 1709053, at *54-56 (Fed. Cl. Spec. Mstr. May 29, 2009), mot. for rev. den'd, 91 Fed. Cl. 126, 134-35 (2010), an analysis of multi-year interval is not needed here. Dr. Rose accepted the proposition that an interval of approximately one month between the vaccination and the onset of symptoms would be an appropriate interval from which to infer causation. See Tr. 620-22.[17]

[17] Dr. Frenkel did not agree. He stated that there is no classic time between the introduction of an antigen to the onset of disease. Tr. 735. Similarly, he also opined that if Bre did not have lupus before the HPV vaccination and if she developed lupus after the HPV (continued…)

Thus, a critical part of the prong-three inquiry is when Bre developed lupus. The parties' conflicting positions are set forth below, followed by an analysis.

Parties' Onset Arguments

Dr. Shoenfeld proposed that Bre fit within the classical amount of time (three weeks) because she received the second dose of the HPV vaccine on August 1, 2007, and presented with a spreading, itchy rash on her body and face on August 23, 2007. Exhibit 1 at 1; exhibit 26 at 4. The report from August 23, 2007, describes Bre's rash as "spreading, itchy….er[y]thematous spots on arms and trunk." Exhibit 26 at 4. Dr. Shoenfeld accepted this rash as a manifestation --- the initial manifestation --- of Bre's lupus. Exhibit 32 at 2-3. In other words, Dr. Shoenfeld sees evidence of Bre suffering from lupus before October 1, 2007, when she was actually diagnosed with the disorder. Exhibit 4 at 13.

The Secretary's experts shared Dr. Shoenfeld's perspective in the sense that Dr. Rose and Dr. Frenkel also viewed Bre's history as consistent with lupus before her actual diagnosis. Dr. Rose and Dr. Frenkel part company with Dr. Shoenfeld, however, because they think Bre could have had lupus even before she was vaccinated. Consistent with the theory that lupus is based in part on genetic factors, Dr. Frenkel stated that Bre could have been suffering from lupus for years before April 2007. Tr. 698-99. The most relevant abnormal health issue was a recurrent rash. Dr. Frenkel cited a report from Bre's pediatrician that she had had a rash for several years. Exhibit C at 2 (citing exhibit 26 at 3 (history of "a macular, raised, itchy rash")).

Furthermore, more than four months before her August 23, 2007 vaccination, Bre presented with a "recurrent rash over complete body." Dr. Vanderburg's recitation of Bre's history was that the recurrent rash was "macular, raised, [and] itchy." Exhibit 26 at 3. Following a physical examination, Dr. Vanderburg stated Bre had "er[y]thematous spots on arms and trunk." Id. at 4. He diagnosed her as suffering from pityriasis rosea. Exhibit 26 at 3. In his expert report, Dr. Rose stated that the treatment record lacks description of a "pattern of distribution or presence of [a] 'herald lesion', two important elements for the diagnosis of [pityriasis rosea]." Exhibit A at 1. Similarly, in his testimony, he averred that he was "suspicious of the rash in April" as evidence that Bre's lupus pre-dated the vaccinations. Tr. 616.

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vaccination, this sequence of events would present a "temporal association," not a "logical causal relationship." Tr. 706.

Agreeing with Dr. Rose, Dr. Frenkel also opined that Bre's April 2007 rash was a manifestation of her lupus. Dr. Frenkel stated that recognizing whether a rash is a sign of lupus is challenging for doctors and, sometimes, a doctor's diagnosis of pityriasis rosea is mistaken. Tr. 694-98. Thus, he opined that "Bre had symptoms of a disease that would later manifest itself [as] SLE months to a couple of years prior to her being diagnosed in September [2007]." Tr. 699-700.

On cross-examination, Dr. Frenkel expanded the basis for his conclusion that Bre suffered from lupus before April 17, 2007. When Dr. Frenkel was asked an open-ended question about what "other sign or symptom" supported his statement that Bre had lupus before vaccination, he referred to laboratory studies of her erythrocyte sedimentation rate ("sed rate" or "ESR"), C-reactive protein ("CRP"), and white blood count. Tr. 700. Later, Dr. Frenkel acknowledged that his report did not mention the results of these tests as a basis for his conclusion about when Bre began suffering from lupus. Dr. Frenkel justified this addition because he "did some more thinking" in preparing to testify. Tr. 721.

Introducing a new basis for an opinion during a hearing is hardly an ideal practice. Dr. Frenkel should have disclosed that the various laboratories studies contributed to his opinion in his report. This disclosure would have permitted Ms. Harris's attorney and Dr. Shoenfeld an opportunity to consider this aspect of Dr. Frenkel's opinion before the hearing. Perhaps in recognition of the omission from Dr. Frenkel's report, the Secretary has not cited Bre's sed rate, etc. as evidence that her lupus existed before the vaccination. See Resp't's Br. at 21-23.

On the other hand, the questioning by Ms. Harris's attorney opened the door for Dr. Frenkel's extra opinion. She did not move to strike this testimony on the ground that it was not contained in his expert report. As such, this testimony remains in the record and it is incumbent upon the special master to consider it. 42 U.S.C. § 300aa—13(a)(1).

The foundation for Dr. Frenkel's opinion is a set of results from various laboratories studies. These are set forth in the following table:

Source	Exhibit 2 at 50-51	Exhibit 3 at 158-60, 167
Date	March 20, 2007 (before vaccination)	Sept. 16, 2007 (after vaccination)
White Blood Count (K/uL), Reference 4.5-13.5	6.87	3.88, marked low

ESR (MM/HR), Reference 0.0-20.	35.0, marked high	49.0, marked high
CRP (MM/HR), Reference 0.0-10.	17.3, marked high	< 3.0

In Dr. Frenkel's opinion, the elevated scores for the sedimentation rate and the C-reactive protein in March 2007, indicate that Bre was suffering from lupus at that time. A commonly used reference guide supports Dr. Frenkel's opinion that elevated sedimentation rates and elevated C-reactive proteins are consistent with lupus. Kathleen Deska Pagana & Timothy J. Pagana, Mosby's Manual of Diagnostic Laboratory Tests (4th ed. 2010) at 197-99, 234-36. In addition, Bre's white blood count was toward the low end of the normal reference range despite her having an infection, which normally leads to an elevated white blood count. Tr. 700; see also Tr. 1113-14 (Dr. Rose's confirmation that lupus can depress white blood counts).

During the rebuttal phase of the case, Dr. Shoenfeld had an opportunity to address the March 2007 laboratories studies. However, his opinion was not clear. He acknowledged that sedimentation rates between 30 and 50 are "accelerated," indicating "mild inflammation." But, without much elaboration, Dr. Shoenfeld opined that a severe inflammatory disease, like lupus, is a consideration when the sedimentation rate exceeds 100. Tr. 937.[18]

Onset Findings

Determining when Bre began suffering from lupus is difficult for at least two reasons. First, as a general matter, lupus presents in many ways. Dr. Shoenfeld stated that lupus is known as the "disease of 1,000 faces." Tr. 194. With such variability, different doctors may detect lupus earlier than other doctors. See Tr. 564 (Dr. Rose).

[18] Dr. Shoenfeld also commented upon the difference between the elevated sedimentation rate and the decreased C-reactive protein in September 2007. In his view and in the opinion of Dr. Rose, these values do not always move in parallel in lupus. Tr. 938-39, 949-54, 1112-13. A rheumatology textbook supports these opinions. Irving Kushner & Stanley P. Ballou, Chapter 52: Acute-Phase Reactants and the Concept of Inflammation, Kelley's Textbook of Rheumatology 771 (Gary S. Firestein et al. eds., 8th ed. 2009).

Second, for Bre specifically, her remote medical history is not as well documented as it could have been. Although Dr. Vanderburg's April 17, 2007 record states that Bre has been having a rash "for several years," there are no records from physicians describing the rash.[19] In addition, there are no photographs of any of the rashes Bre experienced that could aid the experts in evaluating her case. Nevertheless, there is sufficient information to evaluate how the evidence preponderates.

The stronger evidence supports a finding that Bre was suffering from lupus, albeit undiagnosed, when she received her first HPV vaccination on April 17, 2007. Several reasons support this finding.

First, Bre presented with a rash on this date. Dr. Vanderburg's description of the rash --- "macular, raised [and] itchy" --- is similar to the advance practice nurse's description of the rash on August 23, 2007 --- "bright spots all over [her] body," "spreading," and "itchy." Compare exhibit 26 at 3 with exhibit 26 at 4. Dr. Shoenfeld accepted the latter description as a manifestation of lupus, but he rejected the former.

Dr. Shoenfeld has a legitimate, yet ultimately unpersuasive, basis for disregarding the April 17, 2007 rash. Dr. Vanderburg stated that Bre suffered from pityriasis rosea. However, as Dr. Rose and Dr. Frenkel explained, the words that Dr. Vanderburg used to describe Bre's rash do not match a typical description for pityriasis rosea. Most notably, there is usually a "herald patch." Exhibit DD (Sidney Hurwitz, Chapter 5: Papulosquamous and Related Disorders, Clinical Pediatric Dermatology (2d ed. 1993)) at 122. But, Dr. Vanderburg did not describe anything like a herald patch. This dissimilarity calls into question the accuracy of Dr. Vanderburg's diagnosis. See Tr. 694-98.

Second, Bre has experienced rashes periodically for years. There was no testimony suggesting that these episodes were also manifestations of pityriasis rosea. Recurrence would be unlikely for pityriasis rosea, which is "self-limiting" and is complete by "14 weeks." See exhibit DD (Hurwitz) at 122-23. However, lupus waxes and wanes with its sufferers experiencing flares unpredictably.

Third, Dr. Rose's presentation was impressive. He appeared to be interested in providing an accurate assessment of Bre's situation, regardless of how his

[19] The Secretary did not specifically request these records and the special master presiding at the time also did not request these records.

testimony would affect the outcome of the case. His opinion that Bre may have had lupus at the time of her vaccination, therefore, carries a great deal of weight. His opinion is meaningful, in part, because his expertise in pediatric rheumatology gives him insights into lupus that other physicians may not have.

A reliance on a specialist's understanding of a disease has precedential support. In Locane, the petitioner unquestionably suffered from Crohn's disease and she claimed that she started experiencing symptoms of Crohn's disease shortly after receiving the hepatitis B vaccine. The Secretary presented the opinion of a doctor who, among other achievements, wrote a book about Crohn's disease. His opinion was that the petitioner was suffering from Crohn's disease before she was vaccinated and this opinion was credited. Locane v. Sec'y of Health & Human Servs., No. 99-589V, 2011 WL 3855486, at *6-8 (Fed. Cl. Spec. Mstr. Feb. 17, 2011). Finding that the special master's decision to credit the Secretary's expert on Crohn's disease was not arbitrary, the Court of Federal Claims denied petitioner's motion for review, 99 Fed. Cl. 715, 726 (2011), and the Federal Circuit affirmed. 685 F.3d 1375, 1380 (Fed. Cir. 2012).

Fourth, the blood tests from March 20, 2007, are consistent with lupus. They show that when Bre was suffering from a MRSA infection, her white blood count, which should have been quite high, was toward the bottom of the normal range. Exhibit 2 at 50-51. Although, as a matter of procedure, Dr. Frenkel should have included this information with his report, Ms. Harris and Dr. Shoenfeld had an opportunity to address it. In his rebuttal testimony, Dr. Shoenfeld acknowledged that the sedimentation rate was high and consistent with "mild" inflammation. Tr. 936-37. Dr. Shoenfeld did not persuasively explain why only mild inflammation was not consistent with someone suffering from lupus.

All these reasons support a finding that Bre had lupus before she was vaccinated. It is important to emphasize that the standard for adjudication is merely a preponderance of the evidence. 42 U.S.C. § 300aa—13; cf. Knudsen, 35 F.3d at 549 (discussing the burden of proof when the Secretary attempts to establish an alternative factor as the cause for a presumed Table injury). If the standard for adjudication were more taxing, then this finding might not be made because much about Bre's condition before vaccination is not known. Nevertheless, there is some evidence about Bre's health before vaccination and this evidence preponderates in favor of finding that Bre was already suffering from lupus before vaccination.

When a disease affects a vaccinee before vaccination, that person may not receive compensation based upon a theory that the vaccine caused the illness. See Locane, 685 F.3d at 1381 (logical to conclude vaccine did not cause the alleged disease when finding that petitioner suffered from the alleged disease prior to vaccination). However, the person may proceed on a theory that the vaccine worsened the pre-existing condition. W.C., 704 F.3d at 1358.

Here, Ms. Harris has not presented any argument based upon a theory of significant aggravation. Although Dr. Rose and Dr. Frenkel expressed the opinion that Bre suffered from lupus before vaccination, exhibit A at 2, exhibit C at 3-4, Dr. Shoenfeld did not present an alternative theory involving significant aggravation in his supplemental reports. See exhibit 118; see also exhibit 119. Similarly, Ms. Harris did not argue for significant aggravation. See Pet'r's Posthr'g Br.

Consequently, the finding that Bre suffered from lupus before receiving the HPV vaccination is another flaw in her case. Even if, contrary to the finding made in section VI. above, she had established that the HPV vaccine can cause lupus, Ms. Harris would be required to establish the appropriate temporal interval. She cannot make this showing and this failure is another reason to deny Bre compensation.

VIII. *Althen* Prong Two -- Logical Sequence

The final aspect of Ms. Harris's causation claim is to establish by preponderant evidence "a logical sequence of cause and effect" showing that the HPV vaccine caused Bre's lupus. Althen, 418 F.3d at 1274. Because Ms. Harris has failed to demonstrate that the HPV vaccine can cause lupus generally, see section VI., above, she cannot be found to have established that the HPV vaccine did cause her lupus specifically. See Caves v. Sec'y of Health & Human Servs., 07-443V, 2010 WL 5557542, at *9-*19 (Fed. Cl. Spec. Mstr. Nov. 29, 2010), mot. for rev. den'd, 100 Fed. Cl. 119, 145 (2011), aff'd per curiam without opinion, 463 F. App'x 932 (Fed. Cir. 2012). Moreover, as explained in the preceding section, the sequence of events (development of lupus followed by vaccination) prevents a finding in Ms. Harris's favor on this prong. See Locane, 685 F.3d at 1381. Nevertheless, for sake of judicial efficiency, the evidence Ms. Harris cited regarding this remaining prong will be discussed.

Ms. Harris relies upon two sources of information to establish this element. First, she cites Dr. Shoenfeld's opinion. Second, she cites a medical record from her treating pediatrician, Dr. Vanderburg. See Pet'r's Posthr'g Br. at 27, 37.

Dr. Shoenfeld's reasoning was that: (1) the HPV vaccine can cause lupus, (2) there is an appropriate and classical temporal association between the second dose of the vaccine and the onset of lupus, and (3) the lack of alternative cause for the lupus. To these factors, Dr. Shoenfeld also added that Bre was genetically predisposed to suffer an autoimmune disease. See Pet'r's Posthr'g Br. at 27. However, the Federal Circuit has rejected this logic as sufficient to meet petitioner's burden of proof under Althen prong two. See Hibbard, 698 F.3d at 1365-66.[20]

Besides Dr. Shoenfeld's opinion, Ms. Harris cites to a record from Dr. Vanderburg, who saw Bre about one year after her diagnosis. In the "history of present illness" portion of the report, Dr. Vanderburg states, "[I]mmun.[ ]reactions she continues to deal with her lupus. [R]heumatology feels that this was brought on by her [G]ard[a]sil shot." Exhibit 26 at 32. The parties have not located any report from a rheumatologist who purportedly stated that the HPV vaccine had caused Bre's lupus. Tr. 663. During the hearing, Ms. Harris elicited testimony from the experts about their understanding of Dr. Vandenberg's note. Tr. 106, 643-44.

In contrast to this unidentified rheumatologist, the Secretary identifies other doctors who treated Bre, were aware that Bre had received the HPV vaccine, but, nonetheless, did not associate Bre's lupus with her previous vaccination. See Resp't's Posthr'g Br. at 23. Significantly, the Secretary also relies upon one doctor who indicated that the HPV vaccine did not cause Bre's lupus. On August 11, 2008, over a year since Bre received her HPV vaccines, Ms. Harris called Bre's neurologist to report a possible seizure and her concern "that symptoms began shortly after having Gard[a]sil injection." Dr. Fulton requested that his nurse "let Mom know that the Gard[a]sil injection/reaction would have taken place 24 to 36 hours after injection." Exhibit 4 at 165-66.

[20] In Hibbard, the petitioner's argument was based upon only the first three points and did not include a reference to "genetic predisposition." However, Bre's genetic predisposition to develop an autoimmune disease also suggests that she was disposed to developing an autoimmune disease without receiving a vaccination.

Taken as a whole, the records of Bre's treating doctors do not persuasively show that they believed the HPV vaccine caused Bre's lupus. Consequently, Ms. Harris has failed to meet her burden of proof for the second Althen prong.

IX. Conclusion

Although Bre's severe disease is regrettable, Congress limited the compensation available from the Vaccine Program to only those people who have demonstrated that a vaccine caused or significantly aggravated an illness. Ms. Harris has not made this showing. Consequently, she is not entitled to compensation.

The Clerk's Office is instructed to issue judgment in accord with this decision.

IT IS SO ORDERED.

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