In the United States Court of Federal Claims

No. 11-355V
(Originally Filed: December 3, 2013)
(Reissued: December 19, 2013)[*]

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C. K., as Mother and Next Friend of V. K.,

Petitioner,

v.

SECRETARY OF HEALTH AND HUMAN SERVICES,

Respondent.

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Vaccine case; off-table claim; *Althen*; petitioner's challenge to the Special Master's decision; HPV vaccine; Gardasil; systemic juvenile idiopathic arthritis

OPINION

Currently before the court is petitioner's motion for review of the Special Master's ruling of May 30, 2013 denying compensation for an injury allegedly caused by a vaccine. The matter is fully briefed, and oral argument was held on October 18, 2013. For the reasons explained below, we deny petitioner's motion for review.

On June 6, 2011, petitioner, C. K., filed a petition for compensation under the National Childhood Vaccine Injury Act, 42 U.S.C. §§ 300aa-1 to-34 (2006) ("Vaccine Act"), on behalf of her minor daughter, V. K. ("V"). The petition alleges that V developed systemic juvenile idiopathic arthritis ("SJIA") because she received two doses of the human papillomavirus

[*] This opinion was initially withheld from publication to provide the parties with a period of time to propose redactions. The court adopted the parties' proposed redactions, which were made to protect petitioner's identity. The opinion is now prepared for release.

("HPV") vaccine. Specifically, petitioner's theory of the case was that the HPV vaccine causes an increase in particular cytokines, the same cytokines are implicated in SJIA, and therefore the HPV vaccine can be a significant factor in causing SJIA. After conducting a hearing, reviewing epidemiological studies, and weighing the evidence provided by the experts, the Special Master concluded that petitioner had failed to establish a persuasive theory of causation and denied petitioner's request for compensation. *See Koehn v. Sec'y of Health & Human Servs.*, No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013) (hereinafter "Decision").

BACKGROUND[1]

I. Facts

V was born in 1995. She was generally healthy throughout childhood. She had no remarkable medical events for the first twelve years of her life other than asthma. Dr. Elena R. Regala, V's routine physician, administered the first dose of the HPV[2] vaccine in February of 2008 during a regular check-up. The brand of HPV vaccine given to V was Gardasil, which is manufactured by Merck.[3] Gardasil provides immunization against four strands of virus: HPV-6, HPV-11, HPV-16, and HPV-18, and is therefore referred to as a quadrivalent HPV vaccine.

The HPV vaccine contains virus-like particles ("VLP") that were created from the L1 protein of the human papillomavirus. In order to generate a robust immune response sufficient to generate long term immunity, the

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[1] The facts are derived from the Special Master's decision.

[2] There are over 130 strands of HPV. Some of these strands cause warts. Two strains of the virus, HPV 16 and HPV 18, are known to cause cancer. For a more thorough description of symptoms caused by an HPV infection, see Decision at *2.

[3] The other brand of HPV vaccine discussed in some of the studies considered by the Special Master is Cervarix, which provides immunity against HPV strands 16 and 18. Cervarix differs from Gardasil in that it provides immunity against only two strains of HPV and contains a lipid and aluminum salt adjuvant known as AS04.

vaccine contains an adjuvant[4] and is delivered intramusculary. This vaccine can cause the host to produce more antibodies than he or she would have produced in response to a natural infection.

The second dose of Gardasil was given to V on April 18, 2008. On or around June 21, 2008, V experienced a rash all over her body. This caused her on June 24, 2008 to visit Dr. Regala, who prescribed Benadryl and prednisone for what Dr. Regala believed to be an allergic reaction. Within three days, V's rash had disappeared. After V stopped taking the prednisone, she developed pain in multiple places including her knees, thighs, and calves. V was admitted to Marian Medical Center on June 28, 2008, for severe joint pain and high fever. While at the hospital, V received medical tests, saw a Rheumatologist, and was prescribed prednisone. On July 2, 2008, she was discharged from the hospital with a presumptive discharge diagnosis of juvenile idiopathic arthritis. At the time she was discharged, V no longer had a fever or joint pain but still had a rash.

The cause of SJIA is unknown. The annual incidence rate of this disease in children less than 16 years of age is between 0.3 and 0.8 out of every 100,000. Children with SJIA exhibit symptoms of arthritis and a recurring fever for at least two weeks as well as a rash, enlargement of the liver or spleen, lymphadenopathy, or serositis. When a child with SJIA has active inflamation, commonly referred to as a flare, he or she may experience muscle pain, pain in more than one joint, a fever, and a rash. SJIA may also cause problems with the heart, liver, or in rare cases, the central nervous system.

Many of the symptoms described above are associated with a dysfunction of the innate immune response and a corresponding increase in the production of pro-inflammatory cytokines. A cytokine is a protein which is released almost immediately by certain cells when they come into contact with a specific antigen. When the cytokine is released it signals other cells to generate an immune response. In short, cytokines are like smoke signals which cells send out to indicate the presence of an invasion and to elicit a defensive response. Respondent's expert testified that the cytokine response

[4] The particular adjuvant contained in Gardasil is amorphous aluminum hydroxyphosphate sulfate, which stimulates antibody production.

is almost universal.[5] There are, however, specific cytokines which are recognized as being either anti-inflammatory or pro-inflammatory. Pro-inflammatory cytokines can lead to fever, increased vascular permeability, and increased synovial inflammation. "The specific pro-inflammatory cytokines that have been implicated in the development of SJIA include interleukin ("IL") 1, IL-6, IL-7, IL-8, IL-18, macrophage inhibitory factor, and tumor necrosis factor [("TNF")]." Decision at *8. Because of the involvement of these cytokines, which are part of the innate immune system, SJIA is classified as an autoinflammatory disease as opposed to an autoimmune disease.[6]

SJIA is treated by medications which minimize inflamation, including some combination of the following: any nonsteroidal anti-inflammatory pharmaceutical such as ibuprofen or naproxen; intravenous immunoglobulin; cyclosporine-A; thalidomide; prednisone, which reduces inflamation and generally suppresses the immune system; etanercept, which targets and inhibits TNF; methotrexate, which is a folic acid inhibitor; tocilizumab, which inhibits IL-6 production; and anakinra, which is a IL-1 inhibitor.

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[5] Scientists have identified approximately 40 specific cytokines thus far.

[6] The distinction between an autoimmune and an autoinflammatory disease is made based on the part of the immune system that is dysregulated or out of balance. The immune system is comprised of two systems: the adaptive and innate. These two systems interact continuously to maintain balance. Hr'g Tr. 67-70, June 21, 2012. When the adaptive immune system is dysregulated, the autoantibodies and autoreactive T cells do not function as they would in a healthy individual and the resultant state is called an autoimmune disease. Rheumatoid arthritis is typically understood to be an autoimmune disease. When the innate immune system, which involves cytokine production by monocytes and neutrophils, functions abnormally, then the resulting state is known as an autoinflammatory disease. *See* Elizabeth D. Mellins et al., *Pathogenesis of systemic juvenile idiopathic arthritis: some answers, more questions*, 7 Nature Revs. Rheumatology 416 (2011) (hereinafter "Mellins"). Before this distinction was made between autoimmune and autoinflammatory diseases, most forms of arthritis were generally referred to as autoimmune disorders. SJIA was only recently classified as an autoimmune disease. Some scholars continue to broadly characterize arthritis as an autoimmune disease and include SJIA in this characterization.

After being discharged from the hospital, V saw a pediatric rheumatologist, Dr. Deborah McCurdy, on July 8, 2008, who noted that V's family history included juvenile idiopathic arthritis and concluded that SJIA was a likely diagnosis in this case. Dr. McCurdy recorded that V's vaccinations were up to date and that V had received two of three courses of the HPV vaccine. Dr. McCurdy communicated these findings to Dr. Regala. When Dr. Regala saw V again on August 19, 2008, she administered the third dose of HPV vaccine. At the time that V received the third course of Gardasil, she was no longer taking prednisone but had started etanercept. A physical therapist recorded that on August 25, 2008, V experienced a flare with symptoms of fever, rash, and increased joint pain. Dr. McCurdy saw V again on September 3, 2008. Dr. McCurdy noted that V complained of having some symptoms after stopping prednisone and that V had swollen ankles and knees. Dr. McCurdy concluded that V had improved but still showed signs of active disease while being treated with methotrexate and etanercept.

Dr. McCurdy continued to care for V through 2010. On January 12, 2011, V visited another pediatric rheumatologist, Dr. Alice Hoftman. During this visit, Dr. Hoftman recommended that V receive the influenza vaccine. Although V had received the influenza vaccine during the previous three years, C. K. refused this treatment for her daughter. Dr. Hoftman recorded that C. K. was hesitant about giving V the vaccine because of Gardasil. Dr. Hoftman explained that there was "'no data but all vaccines and infections can trigger autoimmune response.'" Decision at *10 (quoting Ex. 5 at 28).

II. Expert Opinions

A. Petitioner's Expert

Petitioner offered the testimony of Dr. Michael J. McCabe, Jr., an expert in the field of immunology. Dr. McCabe is not a medical doctor and does not treat patients. In his report, Dr. McCabe wrote that the cause of arthritis is multi-factorial. Genetic susceptibility and environmental triggers such as infections and vaccinations are possible causative factors. Dr. McCabe's theory is essentially that the HPV vaccine, which Dr. McCabe characterized as a potent immunogen, was the environmental trigger that caused V's immune system to fall out balance resulting in her SJIA. The evidence of this is that the vaccine elicited a strong cytokine response which involved the same cytokines that are associated with SJIA.

In support of his theory, Dr. McCabe provided "'scientific and medical literature that implicates pro[-]inflammatory cytokines and inflammatory responses and innate immunity in the pathogenesis of systemic juvenile arthritis.'" Decision at *12 (quoting Hr'g Tr. 123). One such article was Ligia A. Pinto et al., *HPV-16 L1 VLP vaccine elicits a broad-spectrum of cytokine responses in whole blood*, 23 Vaccine 3555 (2005) (hereinafter "Pinto"), which Dr. McCabe interpreted as showing an increase in the production of particular cytokines in response to the HPV vaccine.[7] The Special Master summarized the Pinto study as follows:

> Twenty-four women participated in the study. Blood specimens were collected before the initial injection, known as month zero. Twenty women, then, received a 50 μg dose of vaccination without adjuvant and four women received a placebo of sterile saline solution. One month later, all women were given a second injection of the same substance (either the vaccination or a placebo). At month two, more blood was drawn. At six months, the women received a third injection. At seven months, more blood was drawn.
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> The researchers determined the level of cytokines for each of the three blood samples after different types of stimulation. This process was done "in vitro," meaning in glass, like a test tube. The blood from women who received the vaccine and women who received the placebo was evaluated in the context of four substances. In the first, the blood was not stimulated at all. The researchers refer to this as the "media." In the second, the blood was stimulated with 10 μg of the virus-like particle present in the vaccine. In the third, the blood was stimulated with 1.0 μg of the virus-like particle. In the fourth, the blood was stimulated with a control known as PHA. The stimulation was for 24 hours in the absence or presence of L1 VLP or PHA.

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[7] The HPV vaccine used in the Pinto study provides immunity against just one strand of HPV, HPV-16, and did not contain an adjuvant. By contrast, the vaccine that V received, Gardasil, provided immunity against four strands of HPV, including HPV-16, and contained an adjuvant.

> . . . . [T]he researchers obtained different results depending upon whether there was any stimulation. For cells in the media–meaning no stimulation–the cytokine levels stayed relatively similar from month zero to month two to month seven. . . . [S]pontaneous secretion of cytokines in the absence of any stimuli (media control) did not show any significant increases following vaccination. For blood that was stimulated either with 10 μg or 1.0 μg of the virus-like particle, cytokines increased. Stimulation of cells from vaccine recipients with L1 VLP (10 μg/ml) induced significant increases in the median levels of inflammatory [] cytokines. Similar patterns of cytokine production to the ones seen in response to L1 VLP at 10 μg/ml were observed when L1 VLP was tested at 1.0 μg/ml.

Decision at *4 (citations and quotations omitted). The Pinto study included a graph that Dr. McCabe used to show how levels of pro-inflammatory cytokines like IL-1 beta, IL-6, and TNF alpha increased in response to direct stimulation with the L1 VLP.[8] Pinto at 3558; *see* Hr'g Tr. 104. According to Dr. McCabe, the particular cytokines that increased in response to the HPV L1 VLP are the same cytokines, IL-1, IL-6, and TNF, that are dysregulated in SJIA. This commonality of cytokines present in response to the HPA vaccine and involved in SJIA is the foundation and mechanistic support for Dr. McCabe's theory of causation.

Dr. McCabe also presented the Special Master with an epidemiological study, which evaluated a database of the medical history of approximately 189,000 women to determine whether these women developed autoimmune conditions within 180 days of receiving the quadrivalent HPV vaccine. Chun Chao et al., *Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine*, 271 J. Intern. Med. 193 (2012)

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[8] This was not the only study Dr. McCabe relied on to show an increase in pro-inflammatory cytokines in response to stimulation with the HPV vaccine. Dr. Pinto participated in a more recent study which also showed "that various cytokines increased after the administration of a vaccine against human papillomavirus." Decision at *12; *see* Alfonso García-Piñeres et al., *Cytokine and Chemokine Profiles following Vaccination with Human Papillomavirus Type 16 L1 Virus-Like Particles*, 14 Clinical & Vaccine Immunology 984 (2007) (hereinafter "García-Piñeres").

(hereinafter "Chao"). One of the diseases that the researchers targeted was juvenile rheumatoid arthritis[9] ("JRA"). In order to identify JRA within the population, the researchers looked for a diagnostic code which included JRA and searched for medications commonly prescribed to treat JRA. While the researchers did not reach any statistically relevant findings regarding JRA, they concluded, "no safety signal for autoimmune conditions was found following HPV4 vaccination in routine clinical use." *Id.* at 202. Dr. McCabe used this study to show that, despite the large population involved in this study, it was not large enough to detect any increase in the rate of SJIA following HPV vaccination because SJIA is such a rare disease. During the hearing, Dr. McCabe explained that there is an absence of epidemiological studies in support of his theory because the disease is too rare for scientists to be able to generate statistically relevant data. Hr'g Tr. 134-35. Dr. McCabe testified that "there is 'no epidemiology that's meaningful enough to inform us' as to whether the HPV vaccine causes sJIA." Decision at *13 (quoting Hr'g Tr. 141-42).

The additional literature which Dr. McCabe relied on in his report to support the connection between vaccines and SJIA was summarized by the Special Master in the following manner:

> Dr. McCabe identified three articles in which the authors stated that infections or vaccinations could be the initial cause for sJIA. Tr. 136, 142-43, 145-46. One article stated, "in juvenile idiopathic arthritis (JIA) a temporal relationship between disease onset, childhood vaccination, remissions and flares hint[s] at a possible relation of JIA disease activity and vaccinations or infections." Exhibit 15 (Arash Ronaghy et al., Vaccination leads to an aberrant FOXP3 T-cell response in non-remitting juvenile idiopathic arthritis, 70 Ann. Rheum. Dis. 2037 (2011)) at 1 [(hereinafter "Roghany")] . . . . Another article asserted that "[o]ne scenario is that infectious agents that are typically encountered in childhood initiate sJIA; no single environmental trigger has been identified, although this lack of an obvious

[9] The researchers did not search for SJIA in particular. However, Dr. Rose believed that "almost certainly all cases of JRA within the study population would have been detected with the methodology utilized by the investigators." Decision at *5 (citations and quotations omitted).

> candidate could point to multiple common agents being capable of initiating sJIA." [Mellins at 417] A third article stated "[i]n juvenile idiopathic arthritis, infections and vaccinations have been suggested as two candidate triggers." Exhibit 12 (Berent Prakken et al., Juvenile idiopathic arthritis, 377 Lancet 2138 (2011)) at 2141 [(hereinafter "Prakken")]. This article continued, "but neither has been confirmed as a trigger because of a scarcity of proper controlled, prospective studies." Id.

Decision at *8 (underlining in original). These articles speculate that there might be a link between vaccination in general and the development of SJIA, but Dr. McCabe suggested that V was most likely predisposed to develop SJIA and that V's environmental trigger, which substantially caused her to develop the disease, was Gardasil. Hr'g Tr. 162, 197.

Dr. McCabe applied the Bradford-Hill criteria for causation to lend credence to his theory. *See* Sir Austin Bradford Hill, *The Environment and Disease: Association or Causation?*, 7 Proc. of the Royal Society of Medicine 295 (1965) (hereinafter "Bradford-Hill"). Dr. McCabe believes that the temporal sequence, the dose-response relationship, biological plausibility, and experimental evidence, all of which are indicative of causation under the Bradford-Hill assessment, showed that Gardasil could cause SJIA. Dr. McCabe acknowledged that some of the Bradford-Hill criteria, such as strength of association and analogy, were not necessarily supportive of his theory of causation.

Regarding the dose-response correlation, Dr. McCabe pointed to evidence that V experienced a flare after receiving the third dose of HPV vaccine. While acknowledging that V was receiving anti-inflammatory treatments when she received the third dose, which made the causation of this flare less than clear, Dr. McCabe suggested that the worsening of symptoms such as fever, rash, and joint pain during this flare showed that V was generating pro-inflammatory cytokines in response to the third dose of vaccination.

Dr. McCabe also noted that studies showed that almost all of the patients who received the HPV vaccine seroconverted, or developed sufficient antibodies for immunity, within seven months. Based on that data, Dr. McCabe concluded that development of disease within seven months after receiving an HPV vaccine was evidence of a proximate temporal relationship.

B. Respondent's Expert

Dr. Carlos Rose, an expert in the field of pediatric rheumatology, testified on behalf of the Secretary of Health and Human Services. As a pediatric rheumatologist, Dr. Rose routinely treats children with SJI–Dr. Rose, however, is not an immunologist, he has not done any research on the HPV vaccine, and he has not researched the role of pro-inflammatory cytokines in SJIA. After reviewing the literature and Dr. McCabe's report, Dr. Rose concluded that it was mere coincidence that V developed SJIA shortly following her second dose of HPV vaccine. Although Dr. Rose acknowledged that there is some overlap in the cytokines, particularly IL-1 and IL-6,[10] present in those recently vaccinated against HPV and those who have SJIA, Dr. Rose concluded that this overlap was more likely due to the limited number of cytokines that are involved in the stereotypical inflammatory response rather than due to a causal relationship with the vaccine.

In response to the research cited by Dr. McCabe regarding the connection between the HPV vaccine and SJIA, Dr. Rose opined that these articles were simply hypothesis-generating and did not represent a scientific consensus based on evidence and testing. Instead, Dr. Rose explained that, in his experience, pediatric rheumatologists generally discuss the safety of HPV vaccine for their patients and are not asserting links between SJIA and vaccines.

Dr. Rose also provided his interpretation of the relevance of the Pinto study. The media group, i.e. the group not stimulated in vitro, was the most relevant to Dr. Rose because it showed a lack of sustained cytokine response one month after each dose of vaccination. Dr. Rose observed that the cytokine response in this media group remained relatively consistent at months zero, two, and seven. This, according to Dr. Rose, is "'very suggestive that the response that this vaccine elicited in these normal people has not been sustained.'" Decision at *17 (quoting Hr'g Tr. 225). By contrast, patients with SJIA experience a pattern of up-regulated cytokines, which is why they are treated with medications that inhibit these specific cytokines. Dr. Rose

[10] "Dr. Rose stated that his experience as a clinician who has seen some (but not all) patients with sJIA improve after taking drugs that control interleukin 1 and interleukin 6 informs his belief that these cytokines play a role in the disease." Decision at *16.

disagreed that the Pinto or García-Piñeres studies showed how a vaccine, which may trigger a temporary cytokine response, can cause permanent cytokine dysregulation resulting in disease.

In support of his assertion that SJIA is not caused by the HPV vaccine, Dr. Rose cited an epidemiological study of roughly 60,000 individuals that found no "evidence of an overall increase in relative risks for autoimmune disorders in participants receiving vaccines containing AS04." Thomas Verstraeten et al., *Analysis of adverse events of potential autoimmune aetiology in a large integrated safety database of AS04 adjuvant vaccines*, 26 Vaccine 6630, 6633 (2008) (hereinafter "Verstraeten") (comparing the development of autoimmune diseases in recipients of three different vaccines, only one of which was an HPV vaccine known as Cevarix, containing the adjuvant AS04 against a control group of recipients of vaccines that did not contain AS04 and finding that there was no greater risk of autoimmune disease in the population exposed to AS04).[11] Dr. Rose believed that this study would have shown a connection between SJIA and the HPV vaccine if one existed.

C. Additional Studies the Special Master Considered

Part of the Bradford-Hill criteria referenced by Dr. McCabe is causation judged by analogy, i.e. whether similar vaccines cause results that are similar to those alleged by petitioner. Bradford-Hill at 299. To explore this criteria of causation, the Special Master looked at analogous studies which evaluated whether there was a connection between SJIA and the meningococcal C vaccine or the measles, mumps, and rubella ("MMR") vaccine. Decision at *22; *see* Marloes W. Heijstek et al., *Safety of measles, mumps, and rubella vaccination in juvenile idiopathic arthritis*, 66 Ann. Rheum. Dis. 1384 (2007) (hereinafter "Heijstek"); Evelien Zonneveld-Huijssoon et al., *Safety and Efficacy of Meningococcal C Vaccination in Juvenile Idiopathic Arthritis*, 56 Arthritis & Rheumatism 639 (2007) (hereinafter "Zonneveld-Huijssoon"). The subjects of these studies already had juvenile idiopathic arthritis or SJIA and

[11] At the hearing, the weaknesses of this study were discussed, including the fact that the study did not involve Gardasil or the adjuvant contained in Gardasil and that the researchers looked for JRA rather than SJIA. Hr'g Tr. 240-44. Dr. Rose also conceded that a proper epidemiological study of SJIA would have to test at least 100,000 individuals because of the rarity of the disease. Hr'g Tr. 245-46.

the researchers sought to determine whether the subjects' disease symptoms worsened after receiving either the meningococcal C or the MMR vaccine. The conclusion was the same in each study: the researchers did not observe any flares or worsening of disease activity in the subjects with SJIA or juvenile idiopathic arthritis following vaccination.

According to Dr. Rose, these studies show that the meningococcal vaccine and the MMR vaccine are safe for use in patients with SJIA. Because of this record of safety, Dr. Rose added that Pediatric Rheumatologists recommend that their patients receive all vaccines, except those containing live viruses. Hr'g Tr. 222.

III. The Special Master's Analysis

In order to receive compensation for an injury caused by a vaccine other than those injuries listed on the Vaccine Injury Table,[12] a petitioner must,

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

Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005); *see* 42 U.S.C. § 300aa-13(a)(1)(A). Petitioner "must provide a reputable medical or scientific explanation that pertains specifically to the petitioner's case, although the explanation need only be 'legally probable, not medically or scientifically certain.'"[13] *Moberly v. Sec'y of Health & Human*

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[12] *See* 42 U.S.C. § 300aa-14(a) (injury table); *W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1356 (Fed. Cir. 2013) (explaining that "[i]n a table claim, the petitioner benefits from a statutory presumption of causation upon showing that the injury is listed in the Vaccine Injury Table for the vaccine received and occurred within the time period in the table" but that "[i]f the injury is not listed in the table, the petitioner must prove actual causation by a preponderance of the evidence").

[13] "[A] finding of causation in the medical community may require a (continued...)

Servs., 592 F.3d 1315, 1322 (Fed. Cir. 2010) (quoting *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548-49 (Fed. Cir. 1994)). The theory presented by petitioner need only be more likely than not and "close calls regarding causation are resolved in favor of injured claimants." *Althen*, 418 F.3d at 1280. "Nonetheless, the petitioner must do more than demonstrate a 'plausible' or 'possible' causal link between the vaccination and the injury; he must prove his case by a preponderance of the evidence." *W.C.*, 704 F.3d at 1356.

If petitioner establishes a prima facie case under the *Althen* elements, then the burden shifts to the government to show "'also by a preponderance of evidence, that the injury was in fact caused by factors unrelated to the vaccine.'" *Id.* (quoting *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 547 (Fed. Cir. 1994)).

The Special Master analyzed each prong of *Althen* in turn. Pursuant to prong one of *Althen*, the Special Master considered whether petitioner presented a reliable scientific theory under the framework of *Daubert v. Merrell Dow Pharmaceutical, Inc.*, 509 U.S. 579, 592-95 (1993), whether petitioner's theory originated within the scientific community or arose for the purposes of litigation, and whether the epidemiological evidence supported petitioner's theory.

First, the Special Master assessed the reliability of Dr. McCabe's theory by applying three[14] of the following *Daubert* factors:

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

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[13](...continued)
much higher level of certainty than that required by the Vaccine Act to establish a prima facie case." *Broekelschen v. Sec'y of Health & Human Servs.*, 89 Fed. Cl. 336, 343 (2009), *aff'd* 618 F.3d 1339 (Fed. Cir. 2010).

[14] The third *Daubert* factor was not considered by the Special Master because neither party introduced evidence regarding the potential rate of error.

community.

Terran v. Sec'y of Health & Human Servs., 195 F.3d 1302, 1316 (Fed. Cir. 1999) (citing *Daubert*, 509 U.S. at 592-95).

In the absence of studies that directly tested petitioner's theory, the Special Master explored the Bradford-Hill causation criteria of analogy. The Special Master considered two types of analogous studies: those that were conducted on animals and those that involved other vaccines. As for the first type, neither party identified a study conducted with animals even though an animal model for macrophage activation syndrome exists, which is similar to SJIA. Dr. Rose explained that the lack of animal studies on this issue was likely attributable to the fact that researchers were pursuing more productive theories. Then the Special Master considered the Heijstek and Zonneveld-Huijssoon studies, which belonged to the second type. These studies showed no disease aggravation when the test subjects who had JIA or SJIA were vaccinated with the meningococcal C or the MMR vaccination. The Special Master wrote that these "studies suggest that when researchers have explored whether vaccinations affect juvenile idiopathic arthritis, they have not found that the vaccine worsens the disease." Decision at *22. The Special Master acknowledged that these studies contained some factual differences from the present case, but concluded that "[b]ecause they are studies, the Heijstek and Zonneveld-Huijssoon findings are entitled to more weight than speculative passages in other articles." *Id.* The Special Master concluded that the analogous evidence weighed against petitioner's case, or was, at best, neutral.

Next, the Special Master observed that Dr. McCabe's theory was unprecedented and had not been published or peer reviewed, although the Special Master noted that Dr. McCabe relied on peer reviewed and published articles in support of his theory. Specifically, the Special Master discussed Dr. McCabe's reliance on the Pinto experiment to show an increase in cytokines seven months after vaccination. Dr. McCabe had drawn that result from the part of the experiment in which researchers had stimulated blood samples from vaccinated individuals with VLP. Dr. Rose agreed with Dr. McCabe that an increase in the cytokine response would follow from direct stimulation with the VLP. However, Dr. Rose opined that the most relevant part of the Pinto study to the present case was the "media" column, which showed that the level of cytokines present in the blood is relatively stable when it is left alone following vaccination. The Special Master found Dr. Rose's interpretation of the Pinto experiment more persuasive. According to the Special Master, this

evidence did not weigh in favor of finding that petitioner's theory is more likely than not.

While the Special Master acknowledged that petitioner had provided the Prakken article, which shows that some scientists may be hypothesizing about a possible link between vaccination and SJIA, the Special Master noted that one equivocal article did not constitute "evidence that the relevant scientific community generally accepts the theory that Gardasil can cause sJIA." Decision at *24. Given that Dr. Rose is the head of pediatric rheumatology at the Alfred I. DuPont Hospital for Children, the Special Master believed that Dr. Rose would know if pediatric rheumatologists were discussing a possible link between Gardasil and SJIA. However, Dr. Rose testified that pediatric rheumatologists were not discussing whether Gardasil caused SJIA. Rather, pediatric rheumatologists, including Dr. Rose, generally recommend that their patients receive all vaccines except those that contain a live virus. The Special Master found that the relevant scientific community, at this time, does not accept the theory that Gardasil can cause SJIA.

Next, the Special Master analyzed the epidemiological studies provided by respondent. One of these articles, authored by Chao, studied the effects of Gardasil in upwards of 189,000 young women. The Special Master noted that the researchers in this study did not find a cluster of autoimmune disease onset in relation the vaccine. The Special Master then turned to the Verstraeten article, which, although he found to be somewhat weak because of the small sample size and because the researchers tested Cervarix instead of Gardasil, "[t]aken together, the Verstraeten and the Chao articles are an additional (but not decisive) reason for finding that Dr. McCabe's theory that a vaccine against human papillomavirus can cause sJIA to be unlikely." Decision at *26.

Lastly, the Special Master noted that Dr. McCabe developed his theory of causation for the purpose of litigation. The Special Master weighed this fact against petitioner's theory under the *Althen* prong-one analysis, which considers whether petitioner has put forth a medical theory causally connecting the vaccination and the injury. After reviewing the totality of petitioner's theory, the Special Master found it problematic that, even if he accepted "the proposition that pro-inflammatory cytokines contribute to the course of sJIA, this observation does not identify the causes of the disease because something must initiate the increase in cytokines." Decision at *8. Ultimately, the Special Master found that Dr. McCabe's theory of causation contained sufficient gaps to make it unpersuasive and petitioner therefore failed to prove

a medical theory that more likely than not the vaccination was causally connected to the injury.

Although the Special Master was not required to reach conclusions about the remaining *Althen* prongs after holding that petitioner had failed to prove prong one, he noted that the record did not support a finding that development of SJIA within a seven-month interval was sufficient to establish a proximate temporal relationship. Specifically, the Special Master found that the Pinto experiment undermined Dr. McCabe's proposed seven-month interval for the onset of SJIA symptoms because the cytokine response to stimulation with VLP was immediate in the Pinto experiment. While Dr. McCabe attempted to explain the delay between vaccination and symptom onset with a theory of amplification, the Special Master saw the media portion of the Pinto study as contradictory because cytokines in this group remained relatively constant over time. Additionally, the Special Master deduced that the evidence provided about V did not persuasively show that she developed SJIA because of the HPV vaccine. After reviewing Dr. McCabe's theory, Dr. Rose's contradictory opinion, and the evidence presented by each expert, the Special Master concluded that petitioner's theory "contain[ed] sufficient gaps to make it unpersuasive." Decision at *26.

DISCUSSION

This court has jurisdiction to review decisions of the special masters in accordance with 42 U.S.C. § 300aa-12. We review the special master's decision under the standard articulated in 42 U.S.C. § 300aa-12(e) and can only set aside "findings of fact or conclusion of law" that were "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 42 U.S.C. § 300aa-12(e)(2); *see Carson v. Sec'y of Health & Human Servs.*, 727 F.3d 1365, 1368 (Fed. Cir. 2013) (describing how the reviewing court should "give no deference to the . . . Special Master's determinations of law, but uphold the Special Master's findings of fact unless they are arbitrary or capricious"). "The arbitrary and capricious standard of review is difficult for [a petitioner] to satisfy with respect to any issue, but particularly with respect to an issue that turns on the weighing of evidence by the trier of fact." *Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1360 (Fed. Cir. 2000). "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." *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1325

(Fed. Cir. 2010). Special masters have discretion to weigh the evidence and "reversible error is 'extremely difficult to demonstrate'" unless the special master has failed to consider the relevant evidence of record, drawn implausible inferences or failed to articulate a rational basis for the decision. *Lampe* 219 F.3d at 1360 (quoting *Hines v. Sec'y Health & Human Servs.*, 940 F.2d 1518, 1528 (Fed. Cir. 1999)). The reviewing court does "not reweigh the factual evidence, assess whether the special master correctly evaluated the evidence, or examine the probative value of the evidence or the credibility of the witnesses–these are all matters within the purview of the fact finder." *Porter v. Sec'y of Health & Human Servs.*, 663 F.3d 1242, 1249 (Fed. Cir. 2011).

Petitioner makes four challenges to the Special Master's decision. We address each allegation in turn.

I. Whether the Special Master failed to consider the record as a whole

Petitioner claims that the Special Master failed to consider the whole record in his decision. *See Dickerson v. Sec'y of Health & Human Servs.*, 35 Fed. Cl. 593, 601 (1996) ("[F]ailure to examine the full record and provide sufficient findings constitutes error."). Petitioner believes that, if the Special Master had considered the entire record, he would have seen that petitioner presented a plausible theory supported by the scientific evidence and research.

Respondent replies that the Special Master did not exclude any evidence and that he considered "all 'relevant and reliable evidence governed by principles of fundamental fairness to both parties'" as evidenced by the thoroughness of his decision. Resp't's Resp. to Pet'r's Mot. for Review 10 (quoting RCFC, App. B, Rule 8(b)(1)). Once the Special Master thoroughly considered the record, he was entitled to weigh the evidence and conclude that he was not persuaded by petitioner's theory of the case.

We agree that the Special Master was careful to consider all relevant evidence, particularly those pieces on which petitioner relied to support her case. The Special Master discussed the literature that Dr. McCabe cited to show that medical experts were considering whether there is a connection between SJIA and vaccination, and he found these articles to be equivocal. *See* Decision at *8. The Special Master reviewed the content of the Pinto study at length and concluded that Dr. Rose's interpretation of the significance

of the study was more persuasive. Decision at *23-24. Additionally, the Special Master engaged each part of Dr. McCabe's expert opinion in the analysis of his decision. The Special Master also considered relevant evidence and testimony provided by Dr. Rose. The fact that the Special Master found Dr. Rose's expert opinion more persuasive in light of Dr. Rose's testimony and scientific evidence is simply a function of the Special Master's role as fact finder. So long as the Special Master considered the relevant evidence, and we conclude that he did, we cannot disturb his findings on this ground.

II. Whether petitioner's burden of proof was erroneously elevated

A. Whether the Special Master required petitioner to provide epidemiological proof

Petitioner asserts that the Special Master erred by requiring epidemiological proof of petitioner's theory. *See Cappizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1325 (Fed. Cir. 2006) ("[R]equiring either epidemiological 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 . . . . impermissibly raises a claimant's burden."). Petitioner acknowledges that, throughout the Special Master's decision, he asserted that he was not requiring epidemiological proof. Nevertheless, petitioner alleges that, instead of accepting Dr. McCabe's explanation for why there is an absence of epidemiological and animal studies connecting Gardasil and the development of SJIA, the Special Master turned to and placed "inordinate emphasis" on epidemiological studies provided by respondent that were not squarely on point. Pet'r's Mot. for Review 25. In sum, petitioner believes that the Special Master de facto required epidemiological evidence by pointing to the Chao article, which did not find any statistically relevant increase in the development of JRA following vaccination with Gardasil, and the Verstraeten article, which involved a different HPV vaccine, a different adjuvant, and did not target SJIA within the studied pool of individuals.

Respondent argues that the Special Master did not raise the burden of proof. Rather, throughout his decision, the Special Master maintained that petitioner must prove her case by a preponderance of the evidence. *See, e.g.*, Decision at *18, *20, *28. Respondent states, and we agree, that under the preponderance of the evidence standard, simply positing a theory is not enough. Petitioner must provide a theory that is persuasive. *See W.C.*, 704

F.3d at 1356.

The Special Master has discretion to assess the reliability of expert testimony when weighing the persuasiveness of the evidence. *Moberly*, 592 F.3d at 1325. While the special master may not require epidemiological proof of petitioner's theory, *Cappizzano*, 440 F.3d at 1325, he may evaluate contradictory evidence provided by respondent, *Stone v. Sec'y of Health & Human Servs.*, 676 F.3d 1373, 1379-80, *reh'g en banc denied*, 690 F.3d 1380 (Fed. Cir. 2012), *cert. denied*, 133 S. Ct. 2022 (2013), and he may consider the presence or absence of peer reviewed scientific studies in the context of applying the *Daubert* framework for analyzing whether an expert's theory is persuasive, *Terran*, 195 F.3d at 1316 (upholding the special master's approach of "using Daubert's questions as a tool or framework for conducting the inquiry into the reliability of the evidence"); *see Cedillo v. Sec'y of Health & Human Servs.*, 617 F.3d 1328, 1339 n.3 (Fed. Cir. 2010) (listing the case law in which the Court of Appeals for the Federal Circuit upheld the special master's application of the *Daubert* factors).

In this case, the Special Master considered epidemiological and other medical articles in the context of assessing the persuasiveness of the expert opinions using the first *Daubert* factor, which is whether the theory has been or can be tested. *See* 509 U.S. at 593. Throughout his analysis the Special Master considered the evidence presented by both experts. After considering the lack of animal studies, the articles that posited about a connection between SJIA and vaccination, and the studies that showed no worsening of symptoms in subjects with JIA and SJIA after receiving the MMR or the meningococcal C vaccine, the Special Master found that the latter evidence was more persuasive than the former and, therefore, this *Daubert* factor was either neutral or balanced against petitioner. While the Special Master may not require petitioner to prove his case with epidemiological studies, that does not mean that scientific evidence that tends to contradict petitioner's theory must be ignored. The Special Master was squarely within his role as a fact-finder when he weighed the evidence presented to him. Because we are not tasked with reweighing the evidence, and the Special Master's conclusion about the first *Daubert* factor was neither arbitrary nor capricious, we find no error. *See Hulbert v. Sec'y of Health & Human Servs.*, 49 Fed. Cl. 485, 490 (2001), *aff'd*, 35 F. App'x 899 (Fed. Cir. 2002) (deferring to the Special Master's determination that the petitioner's expert did not present an opinion that was as credible as the opinion given by the respondent's expert when analyzed under the *Daubert* framework).

B. Whether the Special Master impermissibly held against petitioner the fact that Dr. McCabe's theory had not been published or peer reviewed

Petitioner asserts the Special Master heightened her burden to something close to scientific certainty by holding against her the fact that Dr. McCabe's theory had not been published and subject to peer review. Rather, plaintiff claims that she met her burden of preponderant evidence by presenting a theory that was in line with published and peer reviewed scientific literature.

Respondent responds that it was permissible for the Special Master to ask whether Dr. McCabe's theory had been published and subject to peer review because it is the second factor of the *Daubert* framework for assessing the reliability of an expert opinion. *See* 509 U.S. at 593. While we agree that it would be problematic if the Special Master had required petitioner uniquely to present a theory that had been tested and peer reviewed, that is not what happened in this case. The Special Master sought indicia of reliability through the use of the *Daubert* framework, and he noted that, "until [V]'s case, there was not even one case report published in the medical journals showing even a temporal sequence in which a Gardasil vaccination preceded sJIA." Decision at *23 (citation omitted). The Special Master did not end his analysis of the second *Daubert* factor there, however. He proceeded to consider the peer reviewed medical evidence presented by petitioner and, after weighing it, concluded, "the evidence relating to peer review and publication does not assist in finding that Dr. McCabe's theory is probable." Decision at *24. The Special Master's finding was not arbitrary or capricious, and it did not impermissibly raise petitioner's burden because it occurred within a larger framework and was not the Special Master's sole reason for concluding that petitioner's theory was unpersuasive.

C. Whether it was in error and raised petitioner's burden when the Special Master considered if rheumatologists generally accept Dr. McCabe's theory

When the Special Master inquired about whether rheumatologist generally accept the theory that Gardasil can cause SJIA, petitioner claims that he impermissibly raised her burden by requiring a theory that is generally accepted within the scientific community. Petitioner cites *Graves v. Secretary*

of Health and Human Services, 101 Fed. Cl. 310, 323 (2011) (reciting that general acceptance of the theory within the medical community is not required). According to petitioner, the Special Master arbitrarily and capriciously relied on Dr. Rose's statement that he did not recall hearing discussion amongst his colleagues about Gardasil causing SJIA.

Respondent contends, and we agree, that the Special Master's inquiry into whether there is general acceptance of Dr. McCabe's theory within the scientific community is permissible as part of the *Daubert* analysis. *See* 509 U.S. at 594. In his analysis of this factor, the Special Master noted that petitioner provided articles, such as Berent Prakken et al., *Juvenile idiopathic arthritis*, 377 Lancet 2138, 2141 (2011), that showed that the scientific community was hypothesizing that vaccinations or infections might trigger SJIA. Decision at *24. Also, the Special Master noted that Dr. Rose testified that pediatric rheumatologists did not accept the theory that Gardasil can cause SJIA and that the general practice of pediatric rheumatologists is to recommend that their patients receive all vaccinations except those that contain a live virus. As between these indications of what the relevant medical community believes about a connection between Gardasil and SJIA, the Special Master found that the relevant scientific community does not generally accept Dr. McCabe's theory. This inquiry, as part of the *Daubert* framework, did not impermissibly raise petitioner's burden of proof

III. Whether the Special Master misinterpreted the Pinto article

Petitioner asserts that the Special Master's findings regarding the Pinto study were contrary to the evidence. First, petitioner alleges that the Special Master was confused in thinking that the Pinto study involved a live strand of HPV. Petitioner points out that there is no evidence of a live human papillomavirus being involved in either V's case or in the Pinto study. The Special Master's statement regarding the live human papillomavirus appeared in the context of the following paragraph in the Special Master's decision:

> Despite contrary testimony from Dr. McCabe . . . , Dr. Rose's focus on the media column is logical. The blood in the media encountered the L1 virus-like particle only in the context of the three doses of vaccination. This pattern resembles what happened to [V] in the sense that no medical record suggests that she was exposed to a living strand of the human papillomavirus. If [V] encountered the human papillomavirus

> after the vaccination, the Pinto article predicts that she would produce a robust immune response like the ones reported for 10 µg and 1.0 µg of the virus-like particle.

Decision at *23. This paragraph, when considered with the Special Master's earlier description of the Pinto study, Decision at *4, shows that the Special Master understood that only VLP was used in the Pinto study. The Special Master's comparison of the reaction of the blood samples when stimulated with VLP to show how the body would react to a natural HPV infection was made to illustrate Dr. Rose's opinion that a robust cytokine response would be expected in response to stimulation. However, the distinction in this case is that V never experienced a stimulant such as a live human papillomavirus or a concentrated dose of VLP as was administered in the Pinto study. This is the reason why Dr. Rose thought that the media group in the Pinto study was more relevant than the stimulated groups. The Special Master's agreement with that analysis was neither erroneous or illogical.

Second, petitioner argues that the Special Master's reliance on Dr. Rose's interpretation of the Pinto study was arbitrary and capricious because Dr. Rose is not an immunologist and has not conducted research involving vaccines or pro-inflammatory cytokines. Dr. Rose was accepted as an expert in pediatric rheumatology and, as such, was qualified to opine about medical studies. The Special Master did not exclude Dr. McCabe's interpretation of the Pinto study, but instead found Dr. Rose's interpretation to be more reliable. *Moberly*, 592 F.3d at 1325-26 ("Assessments as to the reliability of expert testimony often turn on credibility determinations, particularly in cases . . . where there is little supporting evidence for the expert's opinion."). Respondent asserts, and we agree, that, in light of all of the evidence, the Special Master's reliance on Dr. Rose's interpretation of the significance of the Pinto study was within his discretion as the fact-finder.

IV. Whether the Special Master arbitrarily and capriciously weighed the evidence against petitioner

A. Petitioner provided scientific support for her theory, which the Special Master arbitrarily dismissed

Petitioner claims that the Special Master erroneously dismissed scientific support for petitioner's theory. Specifically, in the Special Master's *Althen* prong-one analysis, he "neither cites not considers the Mellins,

Roghany, Prakken, or Emeny articles."[15] Pet'r's Mot. for Review 20. Petitioner argues that, instead of affording proper weight to the aforementioned studies provided by petitioner which were relevant, from respected journals, and peer-reviewed, the Special Master arbitrarily favored analogous, but off-topic, studies authored by Heijstek and Zonneveld-Huijssoon. Petitioner distinguishes the Heijstek and Zonneveld-Huijssoon studies because they involved the meningococcal C and the MMR vaccines, which lack the potency of Gardasil, and involved patients who had already developed SJIA and may have been taking pharmaceuticals to control the disease. Additionally, Dr. McCabe testified that he would expect the meningococcal C vaccine, which is a vaccine against a bacterial infection, to elicit a different cytokine response than the HPV vaccine, which immunizes against a virus. Hr'g Tr. 183-84. These differences between the Heijstek and Zonneveld-Huijssoon studies and the facts of this case, according to petitioner, make the Special Master's reliance on them arbitrary and capricious.

By contrast, respondent argues that the Special Master considered the Prakken, Mellins, Roghany, and Emeny articles but found that they did not support petitioner's theory. While the Special Master did not evaluate each of these articles specifically in the context of prong one, he did reference them throughout his decision and found that the statements that petitioner relied on from these articles were ambiguous. In his decision, the Special Master described the scientific support that petitioner gleaned from the Prakken, Mellins, and Roghany articles and found it to be unpersuasive due to the equivocation in the findings. Decision at *8-9, *13, *16, *22, *24. While the Special Master only briefly mentioned the Emeny article in his decision, he did write that, "[a]t the hearing, relatively little attention was paid to the García-Piñeres article, Emeny article, or the Evans article because Dr. McCabe and Dr. Rose primarily discussed an article by Pinto." Decision at *3. As fact-finder, it is within the province of the Special Master to weigh the evidence and determine whether it is reliable. He plainly was aware of all the articles and was not obligated to unpack them in detail. His treatment of the Prakken, Mellins, Roghany, and Emeny articles was not arbitrary or capricious.

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[15] The "Emeny" article referred to in the quotation above is Rebecca T. Emeny et al., *Cellular Immune Responses to Human Papillomavirus (HPV)–16 L1 in Health Volunteers Immunized with Recombinant HPV-16 L1 Virus-Like Particles*, 188 J. Infectious Diseases 327, 336 (2003) (hereinafter "Emeny").

B. Whether the Special Master arbitrarily and capriciously disregarded Dr. McCabe's testimony

According to petitioner, the Special Master erred by disregarding Dr. McCabe's testimony on prong two because he does not treat patients. Petitioner asserts that Dr. McCabe is qualified to testify about causation even though he would not be qualified to testify about treatment. Petitioner also opines that, while Dr. McCabe was uniquely qualified to testify about the causal connection between Gardasil and SJIA based on his research as an immunologist, Dr. Rose has never focused on causation but instead specializes in treating children with SJIA.

Respondent replies that the Special Master fully considered Dr. McCabe's testimony, including Dr. McCabe's testimony concerning whether V's flare following the third Gardasil dose was indicative of specific causation. Respondent points out that it is the Special Master's prerogative under the law to examine the qualifications and expertise of the witnesses when weighing their opinions, citing *Locane v. Secretary of Health and Human Services*, 685 F.3d 1375, 1380 (Fed. Cir. 2012). Here, the Special Master found more reliable Dr. Rose's opinion that V's vaccination with Gardasil and development of SJIA were unrelated events. This finding is sound under the law and was not arbitrary or capricious given the divergent expert opinions.

Finally, petitioner contends that the Special Master erred by disregarding Dr. McCabe's testimony about the temporal relationship between vaccination and disease. Dr. McCabe explained that a cytokine response may take months to cycle through a period of amplification to eventually manifest as SJIA. Dr. McCabe testified that development of SJIA within seven months of vaccination therefore would be a medically appropriate period for causation because that is the time period when the immune system works to create antibodies against HPV in response to the HPV vaccine. *See* Decision at *27. Timing was thus indicative of causation in V's case, according to Dr. McCabe, because she developed SJIA within four months of her first dose and two months of the second dose.

The Special Master was not persuaded by Dr. McCabe's explanation of the amplification process. "[S]pecifically, Dr. McCabe did not explain why the immune system's production of cytokines would be amplified for weeks and months without a stimulant being present." Decision at *28. The Special

Master found that Dr. McCabe failed to explain how a seven month period is appropriate for causation based on a theory involving the cytokine response when both experts agree the response is almost immediate to an antigen or trigger. The Special Master wrote that "[t]he body's rapid cytokine response appears inconsistent with Dr. McCabe's assertion that the onset of disease could take many months." Decision at *28.

Respondent argues that the Special Master was entitled to find persuasive Dr. Rose's opinion regarding timing, which was that the medically appropriate period for causation should be short if the cause is cytokine related. Dr. Rose's opinion was not the only scientific evidence that suggested a shorter window for causation than Dr. McCabe proposed. The Special Master also drew from data in the Pinto study showing increased cytokines in response to stimulation and compared it to data that demonstrated a low and consistent level of cytokines in the absence of stimulation. The Special Master found that "[t]he Pinto experiment [] undermines the cohesiveness of Dr. McCabe's theory, particularly in regard to timing both for onset of symptoms and duration of symptoms." Decision at *23.

After considering the evidence and testimony from both experts, the Special Master asserted that a finding on *Althen* prong-three was not necessary because petitioner had failed to establish prong-one. Nevertheless, the Special Master noted the following: "In the absence of evidence, it is difficult to find that [petitioner] has met her burden of proof. Even two months is probably too long an interval for a cytokine-driven reaction." Decision at *28. We will not disturb this finding because it was not arbitrary or capricious in light of the evidence.

CONCLUSION

It is not our role to "reweigh the factual evidence, assess whether the special master correctly evaluated the evidence, or examine the probative value of the evidence or the credibility of the witnesses." *Porter*, 663 F.3d at 1249. Because the Special Master's decision was not arbitrary, capricious, or otherwise not in accordance with the law, we affirm his decision. For the reasons set forth above, we deny petitioner's motion for review. The clerk is directed to enter judgment accordingly. No costs.

s/Eric G. Bruggink
ERIC G. BRUGGINK
Judge