

March 26, 2020

Secretary Alex M. Azar II
Secretary of Health and Human Services
Office of the Secretary
330 C St SW
Washington, DC 20416

RE: National Vaccine Injury Compensation Program: Revisions to the Vaccine Injury Table;
Notice of Proposed Rulemaking

OPEN LETTER TO THE SECRETARY

Dear Secretary Azar,

I am writing to express my disagreement with the proposed rulemaking as it relates to the revision to the Vaccine Injury Table. Specifically, Shoulder Injury Related to Vaccine Administration (SIRVA) should not be removed from the Vaccine Injury Table. On the other hand, I agree with the proposed removal of vasovagal syncope. The scientific literature and my experience, education, and training support SIRVA as a table injury.

By way of background, I am an orthopedic surgeon on the faculty of Johns Hopkins School of Medicine where I am the Shoulder Fellowship Director. The views expressed in this letter reflect my own opinion and I speak only for myself. In addition to my teaching duties, I see approximately 2500-3000 patients each year for shoulder issues, and I perform 400-500 shoulder surgeries annually. I am an active academician with teaching and research responsibilities. I peer review journal articles for multiple orthopedic journals having to do with shoulder disorders.

The evidence supports that both vaccine antigen *and* injection into or near the bursa or synovium are required to cause SIRVA. This is in contradistinction to vasovagal syncope that is a response to the needle or the injection itself and has nothing to do with vaccine antigen. Vasovagal syncope can and does occur routinely with various injections that do not contain any vaccine antigen (they also occur with aspirations-removal of fluid, or blood draws). SIRVA does not result from the 'trauma' of the needle being close to or within the bursa or synovium; rather bursitis and synovitis are directly caused by the vaccine antigen delivered by the needle. I do not agree with the IOM report suggesting "the injection, and not the contents of the vaccine, contributed to the development of deltoid bursitis" (this is causal fallacy). While it is true the scientific community believes the risk of SIRVA is greatest with inappropriate deep and 'high' administration, the fact remains that antigenic material is required to elicit a typical SIRVA injury.

In other words, the mechanism of causation is an immune-mediated inflammatory reaction to **antigenic material** injected into or near the synovium or bursa. While needle injection is *necessary* to deliver the antigen into these structures, it is not *sufficient* to cause bursitis or synovitis alone. Also, antigen within the skin or muscle does not cause SIRVA, rather both the needle injection into the synovium or bursa *and* the antigen are required to cause SIRVA. If there was a way to get antigen into the bursa or synovium without the needle this would likely cause SIRVA.

There are multiple peer-reviewed articles that support the theory on how vaccinations can cause shoulder injuries. One of the first published articles was in 2007 by Bodor and Montalvo in the well reputed medical journal *Vaccine*. [Bodor, M., & Montalvo, E. (2007). Vaccination-related shoulder dysfunction. *Vaccine*, 25(4), 585-587.] They present two cases of shoulder pain, decreased range of motion, and weakness after vaccine injection. Notably, both cases involved injections 'high' (within 1-2 cm of the acromial bone) into the deltoid muscle with symptoms beginning two days after injection. In this report, they investigated the distance of the subacromial bursa from the skin in their 2 patients and 21 healthy controls. They found the skin to subacromial bursa to be .8 to 1.6 cm. A typical needle length used in injections is 1 inch or 2.5 cm. They further found the extent of bursa ranged from 3.0-6.0 cm from the acromion. They hypothesize that in their two patients the vaccine was injected into the subacromial bursa, "causing a robust local immune and inflammatory response." One patient developed adhesive capsulitis or frozen shoulder and both patients developed pathology of multiple shoulder structures including the subacromial space, biceps tendon, and the glenohumeral joint. This suggested to the authors, and plausibly so, the origin of pain to be from an inflammatory response rather than needle injection alone or an overuse mechanical injury.

Lippert further investigated needle length used for injections, albeit in a pediatric population, determining an 11-61 percent risk of over-penetration when using needle lengths recommended by the Centers for Disease Control.

The pivotal article is by Atanasoff and is also published in *Vaccine*. [Atanasoff, S., Ryan, T., Lightfoot, R., & Johann-Liang, R. (2010). Shoulder injury related to vaccine administration (SIRVA). *Vaccine*, 28(51), 8049-8052.] The research came out of the Department of Health and Human Services and the University of Kentucky School of Medicine. It builds upon the findings of Bodor and Montalvo by reviewing the claims in the Vaccine Injury Compensation Program database from 2006-2010 for shoulder injury. 13 cases were found where 46% again reported a vaccination high in the deltoid. Further the pain began within 24h for 93% of patients with findings of limited range of motion or painful motion. 1 patient did have pain beginning within 4 days of injection. Atanasoff et al concludes based on their work and the prior literature that a vaccine antigen injected into synovial tissue has "the potential for inducing a prolonged immune-mediated inflammatory reaction." They base their theory of causation by considering specificity, temporal association, biological plausibility, coherence, and experimental evidence (this approach adds to the reliability of the theory). All patients received a vaccine with a rapid onset of symptoms, no history of shoulder pain or prior dysfunction, with symptoms isolated to the area of injection, with physical findings consistent with a local immune-mediated

inflammatory injury, and finally with many, but not all, recalling a mechanism that could support injection of antigenic material into the bursa (high deltoid).

It is important to note that simple needle injection without antigenic material with other agents such as lidocaine or platelet rich plasma, have not been associated with shoulder injuries. Lidocaine injections and platelet rich plasma or bone marrow aspirate injections into the bursa or synovium are incredibly common in medical practice. This lends further support and reliability to the theory that antigenic material (not simply any type of material) is the likely cause of immune mediated inflammation as the cause of SIRVA (specificity criteria of causation). The criteria of reversibility is also established in that if the proposed cause is removed (antigenic material), the effect SIRVA is not seen (no similar issues with lidocaine and other injected materials).

Atanasoff further cites animal studies that have demonstrated the basic science plausibility of inflammation that was immune mediated [Dumonde, D. C., & Glynn, L. E. (1962). The production of arthritis in rabbits by an immunological reaction to fibrin. *British journal of experimental pathology*, 43(4), 373.]. A human study of volunteers also explored the reaction to vaccine injected into the joint [Trollmo, C., Carlsten, H., & Tarkowski, A. (1990). Intra-articular immunization induces strong systemic immune response in humans. *Clinical & Experimental Immunology*, 82(2), 384-389.] In this study 6 healthy volunteers had influenza vaccine injected into the knee (5) and wrist (1) with 14 day follow up. As this was primarily a basic science study, the clinical follow up was limited. However, all six developed joint swelling and stiffness. The authors do not report pain and vaguely described these symptoms as “disappearing in some days.” They conclude that “the influenza virus antigen deposited in the joint space induces strong systemic antibody response” and that this response was significantly higher than the control group that received subcutaneous injections.

These studies add to the reliability of the theory via the criteria of ‘experiment’ based evidence). The ‘coherence’ criteria of causation is also established as experimental lab studies are consistent with epidemiologic reports.

Additionally, like Bodor and Montalvo, Atanasoff suggests the rapid onset of pain with limited motion is likely associated with an immune reaction to a previously sensitized shoulder, rather than typical mechanical etiologies of shoulder pain or a result of needle injection alone.

The report by Arias et al in 2017 in the Journal Vaccine lends additional reliability to the theory and provides the best evidence as to feasible timeframe for the development of SIRVA [Arias, L. M., Fadrique, R. S., Gil, M. S., & Salgueiro-Vazquez, M. E. (2017). Risk of bursitis and other injuries and dysfunctions of the shoulder following vaccinations. *Vaccine*, 35(37), 4870-4876.]. In this study, a systematic review of the literature and a review of the Spanish Pharmacovigilance System database (FEDRA) was conducted. They found a total of 45 cases-the largest series to date- (including the 15 reported by Bodor and Atanasoff) - with a majority reporting pain within 48 hours with a range from immediate to within 2 months. The most common diagnosis was bursitis and tendonitis. They also report a great number of cases

reporting a high injection location. **[The comment in the rule making document when citing Arias is misleading and incorrect]** Again, the authors surmise the cause to be an immune mediated response of inflammation related to antigens or adjuvants injected into the bursal tissue, likely from poor technique related to various factors (site, needle choice, angle and location of injection, not accounting for patient size variation), not needle or injection technique alone. Interestingly, the authors confirm the male to female ratio of 0.41, consistent with prior reports as well as VAERS database from 2010-2012 recording a ratio of 0.31, and the French National Pharmacovigilance database reporting a 0.34 ratio. The fact that females are equally or less likely than males to receive vaccinations, yet represent the majority of injured patients lends additional credence to the theory as females smaller body mass and muscle bulk would be expected to result in a higher rate of inadvertent injection into the bursa (this supports the 'biological gradient' criteria for causation).

Biologic gradient is another criteria that is used to support theories of causation. In other words, a dose-response relationship would be expected to result in a greater incidence of the injury. In this case we have seen in the literature a link to the frequency of high deltoid injection with a greater likelihood of injury. And as Arias reported a greater likelihood for females with smaller muscle mass to be more likely to develop an injury.

These studies taken together add further reliability to the theory, as independent researchers from separate institutions, different geographic locations (continents), different sample sizes, and different time periods (2007-2017) have come to similar conclusions (additional criteria for supporting causation is that of 'consistency').

This theory does have growing acceptance as evidenced by documents from the CDC "You Call The Shots-Make sure vaccination is safe" indicating the 'safe' zone for injection with instructions to inject into the 'middle' of the thickest part of deltoid muscle (avoiding the 'high' at risk area). [https://www.cdc.gov/vaccines/hcp/infographics/ycts-shingrix.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fvaccines%2Fhcp%2Finfographics%2Fyou-call-the-shots-intramuscular-shingrix-vaccination.html]. Similarly, in a publication in the Journal of the American Pharmacists Association, Foster et al provide appropriate guidelines for location (middle deltoid, selecting needle sizes for different individuals, angle of entry) of an appropriate vaccine injection [Foster, S. L., & Davis, M. V. (2013). Vaccine administration: preventing serious shoulder injuries. *Journal of the American Pharmacists Association*, 53(1), 102-103.]. There would be no need to localize injections to the middle of the deltoid if the theory of causation related to SIRVA did not have merit.

Suggesting that SIRVA likely results from poor vaccination technique, **rather than** an antigen [Rulemaking document under header Scientific Literature Concerning SIRVA and Vasovagal Syncope] is incorrect. It would be correct to say the literature supports that poor injection technique **of antigen** is the cause of SIRVA.

In the section titled 'Reason for Removal of SIRVA and Vasovagal Syncope', additional reasons suggest that SIRVA is preventable with proper technique alone. While I agree there are simple,

reproducible and reliable methods to prevent vasovagal reactions (patient can remain in a chair or easily lie down if beginning to feel like they may faint), such measures will not prevent SIRVA. As described, many sources over many years (CDC, Pharmacy, Nursing) have taught appropriate techniques to their providers to help minimize SIRVA. Despite the steps taken to appropriately administer vaccine into the deltoid muscle (appropriate needle size and location) there remains a strong likelihood there is antigen injected deep beyond the muscle into the bursa or synovium in some cases.

This is supported by the literature, as there is not a universal reporting that only ‘high’ injections resulted in SIRVA (Bodor, Atanasoff, Arias). Despite years of advocacy and training for appropriate injection sites and needle sizes, SIRVA remains an issue. All patients can be seated or lie down to prevent injury from a vasovagal response. For a variety of reasons, not all injections can be perfectly administered by even the best trained and experienced practitioners (patients vary greatly in their size and shape, and providers can’t be 100% certain of the location of the tip of the needle). Practitioners are fundamentally interested in doing ‘no harm’; to suggest our motivation to take precautions comes from the lack of risk associated with VICP no-fault claims is simply outrageous.

It is not practical nor cost-effective to institute measures to ensure that the injection does not reach the bursa or synovium. In order to guarantee this, imaging guidance (ultrasound) would have to be used by all providers providing injections. This is beyond the expertise of nurses and pharmacists that routinely administer these shots. The healthcare system does not have enough physicians skilled in this practice to deliver the necessary vaccinations each year. Further, the costs would be prohibitive and likely promote racial and socioeconomic disparities in terms of access to image guided injections.

There is also tremendous risk should this injury have to be covered by malpractice insurance and this could unnecessarily drive up the costs of delivering vaccines and reduce the number of people willing to administer them. The program was created specifically to overcome the limitations and difficulties of civil litigation as well as the ramification of increased litigation against pharmaceutical companies (higher liability insurance, limited supply or exorbitant pricing, or even interest in vaccine development). Considering the current COVID pandemic crisis, shifting the risk to private providers and pharmaceutical companies does not seem to be a reasonable proposal. When a COVID vaccine is developed and distributed, there will be many more vaccinations administered, likely including to children. This would appear to be a very unwise time to delete SIRVA from the Vaccine Injury Table. Instead of removing an appropriate injury (SIRVA) from the table, processes could be improved to facilitate efficient review of SIRVA cases. One such suggestion is to have the program’s SIRVA cases reviewed by an independent expert committee of physicians to determine those that have merit and meet the criteria outlined in the table’s Qualifications and Aids to Interpretation for SIRVA.

The suggestion that some individuals use information inappropriately and mislead the general public is simply not a good reason to remove a legitimate injury from the table. Misinformation should be fought by promulgating good, reliable information.

In summary,

1. **The scientific evidence does support a causal relationship between injection of vaccine antigen and SIRVA.** SIRVA should remain a table injury and the evidence is summarized above.
2. The policy reasons to remove SIRVA are weak and the policy reasons to keep SIRVA are much stronger, summarized above, and maximize the net benefits related to economic, public health, safety, and equity issues.

Atanasoff, S., Ryan, T., Lightfoot, R., & Johann-Liang, R. (2010). Shoulder injury related to vaccine administration (SIRVA). *Vaccine*, 28(51), 8049-8052.

Arias, L. M., Fadrique, R. S., Gil, M. S., & Salgueiro-Vazquez, M. E. (2017). Risk of bursitis and other injuries and dysfunctions of the shoulder following vaccinations. *Vaccine*, 35(37), 4870-4876.

Bodor, M., & Montalvo, E. (2007). Vaccination-related shoulder dysfunction. *Vaccine*, 25(4), 585-587.

Dumonde, D. C., & Glynn, L. E. (1962). The production of arthritis in rabbits by an immunological reaction to fibrin. *British journal of experimental pathology*, 43(4), 373.

Foster, S. L., & Davis, M. V. (2013). Vaccine administration: preventing serious shoulder injuries. *Journal of the American Pharmacists Association*, 53(1), 102-103.

Iyer, S., & Kim, H. J. (2016). Cervical radiculopathy. *Current reviews in musculoskeletal medicine*, 9(3), 272-280.

Trollmo, C., Carlsten, H., & Tarkowski, A. (1990). Intra-articular immunization induces strong systemic immune response in humans. *Clinical & Experimental Immunology*, 82(2), 384-389.

Sincerely,



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All opinions expressed are solely my own and do not represent or reflect the views of the Johns Hopkins University or the Johns Hopkins Health System