

# All Magic Comes with a Price: A Case of Henoch-Schönlein Purpura Post-influenza Vaccination

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**KEY WORDS:** adjuvants, Henoch-Schönlein purpura (HSP), influenza, vaccine  
*IMAJ* 2020; 22: 582-583

Immunologic reactions to safe and effective vaccinations raise concerns for both treating physicians and patients. In modern medicine, vaccinations remain one of the best public health measures preventing spread of infectious diseases; however, growing apprehension about risks of vaccination have been associated with concerns regarding outbreaks of vaccine-preventable diseases [1,2]. Vaccine safety assessment depends on population based background analysis failing to account for interindividual factors including genetic predisposition to immune hyperstimulation, autoimmunity among other factors.

This issue of the *Israel Medical Association Journal (IMAJ)*, contains a case report by Kantor and colleagues [3] describing a case of Henoch-Schönlein purpura (HSP) post-influenza vaccination. In their report, the authors describe the case of a 4-year-old girl with past medical history only significant for seasonal urticaria including a rash spreading over the trunk and both upper and lower extremities. Given the characteristic appearance of the rash, microhematuria, and supporting lab findings, a diagnosis of HSP, as defined by the American College of Rheumatology, was made. Ruling out other possible causes of rash in this

young patient, the authors highlighted the administration of flu jab 8 days prior to presentation.

Several publications report vasculitides following influenza vaccination, the majority of which are small vessel vasculitis [4-7]. HSP cases following influenza showed a latency between vaccination and disease development of 1 to 22 days with an average of 12 days. Most patients developed the characteristic clinical picture after receiving one dose of vaccination; however, others developed an immune response after re-challenging with another dose of vaccination. Patients with past medical history significant for HSP, drug eruptions, or allergies to food components were most at risk [4,8-10]. Triggers to HSP remain unclear; however, association between drugs, infections, and vaccination have been suggested [11,12].

In a case control study comprised of 288 cases and 617 controls, vaccination with measles-mumps-rubella was associated with increased risk of HSP (odds ratio [OR] 3.4; 95% confidence interval [95%CI] 1.2-10.0), raising the possibility of a vaccine administration acting as a trigger to disease development [13].

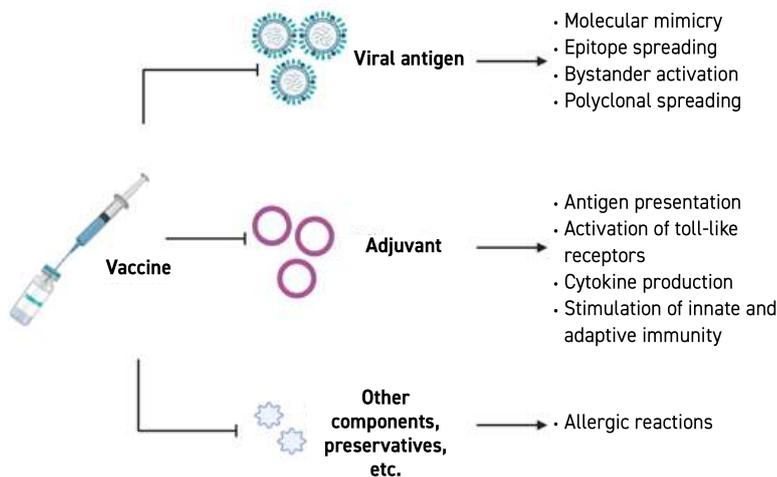
Another line of evidence can be deduced from exploring the vaccine adverse event report system (VAERS) for reports on HSP post-seasonal flu vaccine. Indeed, close to 90 events were retrieved with onset intervals ranging between a day and 60 days while the majority of cases onset was within the first 15 days.

Similar to published peer reviewed reports, multiple case studies had documented history of heightened immune response, including reactive airways diseases, eczema, seasonal allergy, and autoimmune disease.

On broader exploration of the immunologic and immune-like adverse reactions to vaccination, it is clear that adverse reactions do not always result from the viral antigen inoculated, but can occur from adjuvants used for vaccine preparation [Figure 1] [14]. Autoimmune diseases and immunologic phenomena usually result from an interplay of factors including genetic susceptibilities, environmental triggers (i.e., drugs, infections) and epigenetic modification [15]. It is well established that viral infections, also vaccines, are capable of hyperstimulating the immune system and result in a response against self-antigen by mechanisms including molecular mimicry, epitope spreading, bystander activation and polyclonal spreading [16]. Perhaps the most established mechanism would be molecular mimicry, where cross reactivity between microorganism antigen and self-antigen result in break of tolerance and mounting to an immune response. In other situations, polyclonal activation of the immune system results in proliferation of B cells and subsequent hyperstimulation of the immune system accompanied with formation of circulating immune complexes resulting in damage to self-tissues.

**Conflict of interest:** Yehuda Shoenfeld appears in U.S. court in vaccine related cases

**Figure 1.** Mechanisms of how vaccine components can induce a heightened immune response in susceptible individuals



Other vaccine components, such as adjuvants, act to enhance antigen specific immune response and might inadvertently result in immune hyperstimulation. Aluminum oxyhydroxide (alum) is widely used as an immunological adjuvant of vaccines. Concerns regarding its use emerged following possible links to macrophagic myofasciitis (MMF) lesions detected in patients with myalgic encephalomyelitis that were characterized by biopersistence of these alum particles in susceptible individuals [17]. Mechanisms of adjuvancy remain elusive. It is postulated that adjuvants promote antigen presentation and consequently enhance the innate and adaptive immune response to antigens [17]. Adjuvants are developed to mimic toll like receptor ligands, thus resulting in activation of toll like receptors and cytokine production and subsequent initiation of innate immune response, which can then activate an adaptive response [18]. In animal studies, intraperitoneal immunization of murine mice with pristane, an oil adjuvant, resulted in systemic lupus erythematosus like disease and arthritis [19]. A similar outcome was reported in Atlantic salmon [20].

**CONCLUSIONS**

The relationship between vaccination and immune disease remains unclear and rais-

es clinical and ethical questions. In the modern era, vaccination remains a cornerstone in the prevention of infectious disease spread due to their effectiveness and safety in most individuals. It is clear that it rests on our shoulders, as physicians, to continue monitoring for side effects and to identify co-factors and individuals at risk of sustaining an adverse reaction from vaccines to prevent those ramifications and to maintain compliance among individuals. The refinement of our approach of vaccine development may eventually lead us to developing safer, and where applicable, personalized vaccines.

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**References**

- Omer SB, Salmon DA, Orenstein WA, deHart MP, Halsey N. Vaccine refusal, mandatory immunization, and the risks of vaccine-preventable diseases. *N Engl J Med* 2009; 360 (19): 1981-8.
- Ledford DK. Henoch-Schönlein Purpura and Influenza Vaccine. *J Allergy Clin Immunol Pract* 2017; 5 (1): 210.
- Kantor R, Galel A, Aviner S. Henoch-Schönlein purpura post-influenza vaccination in a pediatric patient: a rare but possible adverse reaction to vaccine. *IMAJ* 2020, 22: 588-90.

- Watanabe T. Vasculitis following influenza vaccination: a review of the literature. *Curr Rheumatol Rev* 2017; 13 (3): 188-96.
- Damjanov J, Amato JA. Progression of renal disease in Henoch-Schönlein purpura after influenza vaccination. *JAMA* 1979; 242 (23): 2555-6.
- Stefanini M, Piomelli S, Mele R, Ostroski JT, Colpoys WP. Acute vascular purpura following immunization with Asiatic-influenza vaccine. *N Engl J Med* 1958; 259 (1): 9-12.
- Liu JY, Wu QS, Liu M, Wang L, Gao YH, Li SS. Henoch-Schönlein purpura nephritis following influenza vaccination: a case report and review of the literature. *Southeast Asian J Trop Med Public Health* 2016; 47 (5): 945-50.
- Watanabe T, Onda H. Henoch-Schönlein purpura with antiphospholipid antibodies following an influenza vaccination. *Pediatr Nephrol* 2001; 16 (5): 458-9; discussion 460-2.
- Blumberg S, Bienfang D, Kantrowitz FG. A possible association between influenza vaccination and small-vessel vasculitis. *Arch Intern Med* 1980; 140 (6): 847-8.
- Damjanov J, Amato JA. Progression of renal disease in Henoch-Schönlein purpura after influenza vaccination. *JAMA* 1979; 242 (23): 2555-6.
- Gonzalez-Gay MA, Calviño MC, Vazquez-Lopez ME, et al. Implications of upper respiratory tract infections and drugs in the clinical spectrum of Henoch-Schönlein purpura in children. *Clin Exp Rheumatol* 2004; 22 (6): 781-4.
- Weiss PF, Klink AJ, Luan X, Feudtner C. Temporal association of Streptococcus, Staphylococcus, and parainfluenza pediatric hospitalizations and hospitalized cases of Henoch-Schönlein purpura. *J Rheumatol* 2010; 37 (12): 2587-94.
- Da Dalt L, Zerbinati C, Straffella MS, et al; Italian Multicenter Study Group for Drug and Vaccine Safety in Children. Henoch-Schönlein purpura and drug and vaccine use in childhood: a case-control study. *Ital J Pediatr* 2016; 42 (1): 60.
- Agmon-Levin N, Paz Z, Israeli E, Shoenfeld Y. Vaccines and autoimmunity. *Nat Rev Rheumatol* 2009; 5 (11): 648-52.
- Sharif K, Watad A, Bridgwood C, Kanduc D, Amital H, Shoenfeld Y. Insights into the autoimmune aspect of premature ovarian insufficiency. *Best Pract Res Clin Endocrinol Metab* 2019; 33 (6): 101323.
- Kivity S, Agmon-Levin N, Blank M, Shoenfeld Y. Infections and autoimmunity--friends or foes? *Trends Immunol* 2009; 30 (8): 409-14.
- Israeli E, Agmon-Levin N, Blank M, Shoenfeld Y. Macrophagic myofasciitis a vaccine (alum) autoimmune-related disease. *Clin Rev Allergy Immunol* 2011; 41 (2): 163-8.
- Israeli E, Agmon-Levin N, Blank M, Shoenfeld Y. Adjuvants and autoimmunity. *Lupus* 2009; 18 (13): 1217-25.
- Satoh M, Reeves WH. Induction of lupus-associated autoantibodies in BALB/c mice by intraperitoneal injection of pristane. *J Exp Med* 1994; 180 (6): 2341-6.
- Koppang EO, Bjerkås I, Haugarvoll E, et al. Vaccination-induced systemic autoimmunity in farmed Atlantic salmon. *J Immunol* 2008; 181 (7): 4807-14.