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Systemic Lupus Erythematosus: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data

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1. Preamble

1.1. Need for developing case definitions and guidelines for data collection, analysis, and presentation for systemic lupus erythematosus as an adverse event following immunization

Systemic lupus erythematosus (SLE) is the prototypic systemic autoimmune disease. It is characterized by the production of autoantibodies which may lead to immune-complex mediated end organ involvement. The incidence of SLE is estimated at 2–7 per 100,000 per year with a prevalence of 12–50 per 100,000 [1]. It is much more common in women and in non-White ethnic/racial groups.

The etiology and pathophysiology of SLE remain poorly understood. As with most autoimmune conditions, SLE is thought to be due to an underlying genetic susceptibility combined with a specific environmental exposure, leading to immune activation and dysregulation. It has been hypothesized that vaccination could be one such environmental trigger [2,3]. Although the susceptibility to SLE is less well characterized, more is known about the pathophysiology of the end organ manifestations of SLE. For example, there is strong evidence that the inflammatory changes in lupus nephritis are due to immune complex formation. These immune complexes activate the complement cascade resulting in significant localized inflammation and tissue damage.

Systemic Lupus Erythematosus can present with a diverse array of clinical symptoms, manifestations and laboratory abnormalities. It is a clinical diagnosis made on the presence of specific clinical and laboratory manifestations; classification criteria are used for inclusion in observational studies and randomized clinical trials. Traditionally the 1997 revised and updated American College of Rheumatology (ACR) classification criteria has been used to define cases for such studies for both adult and pediatric SLE [4]. The Systemic Lupus International Collaborating Clinics (SLICC) group recently proposed and validated an expanded classification of SLE [5]. Both the traditional ACR and the newer SLICC criteria include immunologic and hematologic laboratory findings as well as clinical manifestations.

Although numerous studies have established the safety of vaccination in patients with SLE, a limited number of published reports describe SLE as a possible complication following routine vaccination. A literature search identified six case reports/series hypothesizing an association between immunization and induction or promotion of SLE; they are summarized in Table 1. Two reports referred to influenza vaccination [6,7], two to human papillomavirus (HPV) vaccination [8,9], and one report describes the

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Table 1
Summary of published reports describing a possible association between vaccination and the onset of Systemic Lupus Erythematosus.

Author, Year Country Article type	Vaccine	Number of Cases Age/Gender/Time interval	Clinical features	Fulfills ACR or SLICC criteria?[a]	Comments
Older et al. [11], [9] US Government Small case series	Various	5 cases:			
	1st case. Typhoid, influenza, meningococcus, tetanus toxoid, Immunoglobulin	31 y/o male One day after vaccines he had an reaction at the site of the typhoid injection; 1 week later he had right arm paresthesia and loss of function	Right arm paresthesia/loss of function, chest pain/pleural effusion, Raynauds, polyarthritis, violaceous rashes, polyradiculoneuropathy, diffuse proliferative glomerulonephritis/LN. + ANA, + dsDNA, low complement, cytopenias. Ongoing symptoms 7 years after diagnosis despite treatment with multiple immunosuppressive medications	ACR: Yes SLICC: Yes	Patient received multiple vaccines simultaneously
	2nd case. MMR, typhoid, influenza, meningococcus, tetanus and diptheria toxoids, oral polio	23 y/o female 2 weeks	Fever, malar rash, alopecia, oral ulcers, pleural effusion. + ANA, + SSA, RNP, Smith, + dsDNA antibodies, low complements. Treated with corticosteroids, lost to follow-up	ACR: Yes SLICC: Yes	Patient received multiple vaccines simultaneously
	3rd case. MMR, typhoid, influenza, meningococcus, tetanus and diptheria toxoids, oral polio	25 y/o male 3 days	Fever, malaise, arthritis, lymphadenopathy, tender gynecomastia, pleural effusions. Mild anemia, increased CK, direct coombs +, + ANA, + dsDNA, increased serum estradiol. Initially treated with oral steroids with improvement, required low term therapy with corticosteroids, azathioprine and methotrexate	ACR: Yes SLICC: Yes	Patient received multiple vaccines simultaneously
	4th case. Typhoid and Hepatitis A	28 y/o female 3 weeks	Oral ulcers, alopecia, polyarthritis, dilated capillary loops, lower extremity weakness + ANA, anti Smith and Anti RNP antibodies, increased CK. Treated with corticosteroids and HCQ with improvement. Started methotrexate 14 months after diagnosis due to persistent symptoms	ACR: Yes SLICC: Yes	Onset of Raynauds phenomenon 3 years prior to SLE diagnosis, ANA testing at the time was negative
	5th case. Anthrax	29 y/o female 12 days after 2nd immunization	Fever, polyarthritis, malar rash, oral ulcers, alopecia, mesangial lupus nephritis. + cytopenias, + ANA, dsDNA, Coombs, anticardiolipin antibodies, low complements. Treated with corticosteroids and HCQ	ACR: Yes SLICC: Yes	No apparent predisposing factor
Hehn et al. [6], [4] Germany Review of spontaneously reported cases	Influenza	1 case of possible SLE found	No clinical information was provided	ACR/SLICC: No case description provided	Not enough detail provided to assess criteria
Agnom-Levin et al. [10], [8] Israel Small case series	HBV	10 cases reported: 8/10 female 56 days after vaccine (mean), days to 1 year (range)	Data are presented in aggregated form. Clinical findings include: Musculoskeletal: 100%, Integument: 100%, Neurologic: 80%, Pulmonary: 70%, Hematologic andRenal: 10%,+ANA: 90%, Other autoantibodies: 90%. Treatment consisted of steroids (80%), HCQ (60%), Various immunosuppressive medications	10 cases All fulfilled ACR criteria per the study author	3/10 patients with prior history of autoimmunity
Morihara et al. [7], [5] Japan Case report	H1N1 Influenza	1 case reported: 77 y/o female 18 days	At age 39, history of rash anemia, positive RF, and negative ANA; At age 77 injection site rash, fever, arthritis, mononeuritis multiplex, +ANA, +anti-ds DNA, low complement Responded to corticosteroids	ACR: Yes SLICC: Yes	Patient history of autoimmunity
Soldevilla [9], [7] Philippines Small case series	HPV	3 cases reported: **1st case**. 17 y/o female 2 months after 2nd vaccine dose	Arthralgias, rash, LN (proteinuria, Class III), + ANA, + anti-dsDNA, low complement. Responded to steroids and cyclophosphamide	ACR: Yes SLICC: Yes	No apparent predisposing factor
		2nd case. 45 y/o female 4 months after 1st vaccine dose	History of RA (11 years), in remission for 1 year, developed fever rash, photosensitivity, arthritis, intestinal pseudo-obstruction, behavioral changes. Brain MRI: vasculitic lesions on frontal lobes. Proteinuria, abnormal sediment, +ANA, +anti-dsDNA, +anti-Ro, +anti-La, +anti-histone, low complement	ACR: Yes SLICC: Yes	Patient history of autoimmunity

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