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Recommendations and Barriers to Vaccination in Systemic Lupus Erythematosus

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Abstract

Patients with Systemic Lupus Erythematosus (SLE) pose a unique dilemma pertaining to immunization against common pathogens. SLE patients are usually not immunized with vaccines based on the fear of either precipitating infection in this immunosuppressed patient population (with live vaccines) or aggravating autoimmunity and hence lupus flares (with any vaccines). However, elevated vulnerability to infection makes patients with SLE precisely the population that needs protection from vaccine-preventable diseases. A summary of guidelines from the Centers for Disease Control and Prevention, professional societies, review articles and expert opinions regarding use of individual vaccines applicable to adults with SLE is presented in this review.

Keywords

Vaccination; lupus

Introduction

The fundamental driver of SLE is an abnormal immune response against self-antigen which is hypothesized to develop in part from exposure to unidentified infectious agents. The aberrant immune response may be mediated by antigen-dependent mechanisms such as molecular mimicry or antigen-independent mechanisms such as interactions between the Toll-like receptors (TLR) of antigen-presenting cells and microbial molecules [1]. At the same time, increased susceptibility to infections in patients with SLE is due to abnormal host

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immune factors such as low complement levels, functional asplenia, and abnormal neutrophil and macrophage response to pathogens [2–5]. Furthermore, the mainstay of SLE treatment is immunosuppressive therapy with medications such as moderate- to high-dose steroids, alkylating agents such as cyclophosphamide, mycophenolate mofetil, azathioprine and hydroxychloroquine which impair immune responses to viral and bacterial infections.

Immunization against common pathogens can potentially be very beneficial in preventing infections in such high-risk patient populations. However, safety and efficacy of vaccines for patients with SLE generate perennial controversy. Concerns are fueled by case reports of *de novo* development of autoimmune disease or flares of existing autoimmune disease after administration of vaccines. In addition, theoretical concerns about inadequate host immune responses to vaccines raise doubts about their effectiveness in protecting patients with SLE from infection. Several inactivated and live, attenuated vaccines, their safety and efficacy, medication effects, and overall recommendations in lupus are discussed here.

1. Pneumococcal vaccine

Invasive pneumococcal disease is associated with significant morbidity and mortality in immunocompromised patients.

1.1 Types

Currently, two types of pneumococcal vaccines are available, a 23-valent pneumococcal polysaccharide vaccine (PPSV23 [Pneumovax, Merck]) and a 13-valent pneumococcal conjugate (PCV13 [Prevnar 13, Wyeth]). PCV 13 contains aluminium phosphate adjuvant. PPSV23 was licensed for use in 1983, replacing the old 14-valent polysaccharide formulation that was first introduced in 1977 [6]. In 2010, PCV13 succeeded the 7-valent conjugate vaccine (PCV7 [Prevnar 7, Wyeth]), covering additional serotypes and further reducing the incidence of otitis media in children and invasive pneumococcal disease in adults [7, 8]. Both vaccines are recommended for use in immunocompromised adults.

Conjugation of the polysaccharide vaccine through protein carriers has enhanced the immunogenicity of the PCV13 vaccine and thereby reduced the disease burden through indirect herd effect. T-helper cell response is generated through protein carriers which are T-cell-dependent antigens, inducing immunologic memory priming, an amnestic response with subsequent reexposure in immunized individuals [9], [10].

1.2 Review of Safety and efficacy

One of the earliest studies by Klippel et al. in 1979 investigated the safety of the PPSV23 vaccine in the SLE population in a randomized, double-blind, placebo-controlled trial at the NIH involving 40 subjects [11]. A year later in 1980, Jarette et al. demonstrated a lower (but still protective) antibody response in SLE patients than healthy controls [12]. Battafarano et al. in 1998 reported safety and efficacy of PPSV23 in a cohort of 73 SLE patients who were given pneumococcal, tetanus toxoid and *Haemophilus influenzae* type B (Hib) vaccines simultaneously. No patient developed a clinically significant lupus flare, while the anti-pneumococcal antibody titers rose by a factor of four in 47% of patients [13]. The good tolerability of this vaccine was confirmed in an Israeli cohort of 24 SLE patients [14] and a

Hungarian study of 18 SLE patients in 2002 [15]. Each of these studies noted concerns about long-term efficacy of the vaccine. About 5/24 (20%) patients in the Israeli cohort did not develop protective antibody titers, while about 26% patients in the Battafarano study had <2-fold increase in antibody titers. McDonald et al. followed serial antibody titers to capsular polysaccharides in 19 SLE patients for three years following immunization with polyvalent pneumococcal polysaccharide vaccine. At three years, eight of 19 (42%) had levels below the threshold of protection [16]. The vaccine has been determined to be safe, with neither generation of autoantibodies nor increase in lupus-related activity [17]. Although a majority of SLE patients did develop protective antibody response, a a significant minority was left unprotected [1, 18].

1.3 Medication effects

The immunogenicity of pneumococcal vaccines in the setting of concomitant immunosuppressive therapy is an area of uncertainty. The immunogenicity of the now-obsolete 14-valent pneumococcal polysaccharide vaccine was studied over a six-month period in 77 SLE patients on oral cyclophosphamide, azathioprine, or a combination of the two drugs in 1985. The investigators determined that the low doses of immunosuppressive medications had no apparent effect on the humoral immune response to the vaccine [19].

A recent study showed that vaccine was safe but poorly immunogenic in patients with SLE. Serum IgG levels against seven pneumococcal serotypes were measured in 54 patients with SLE four to six weeks after receipt of PPSV23. Most subjects were on low-dose prednisone; 28 were receiving additional immunosuppressive agents, including mycophenolate mofetil, cyclophosphamide or azathioprine, and 26 were on no additional immunosuppression. Serotype-specific response rates were not significantly different between the two groups; however, the mean ratio of pre- and post-immunization antipneumococcal antibody titers was higher in the group with no additional immunosuppressive therapy. Overall fewer than 40% of patients had adequate immune responses to the vaccine, as determined by fourfold increase in at least 70% of serotype-specific IgG responses. The cohort was too small to discriminate the impact of the individual immunosuppressive drugs [20].

Although conjugate vaccines are more immunogenic in children than polysaccharide vaccines, there are to date no published studies comparing the immunogenicity of PCV13 and PPSV23 in adult patients with lupus. A recent multicenter, placebo-controlled trial randomized 46 SLE patients to receive PCV7 or placebo at baseline followed by PPSV23 at 24 weeks, assessing antibody responses to serotypes shared by both vaccines. Responses to the combination of PCV7 followed by PPSV23 were not superior to responses to PPSV23 alone [21]. Future studies are needed to compare PCV13 and PPSV23 combinations and different schedule designs.

In other autoimmune diseases, such as rheumatoid arthritis, methotrexate alone or in combination with TNF inhibitors has been reported to decrease the immunogenicity of the pneumococcal vaccine [22, 23]. However, there are no such data in the lupus patient population.

In summary, pneumococcal vaccine is safe but may be weakly immunogenic in patients with SLE on immunosuppressive medications.

Recommendation—The U.S. Center for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) guidelines for adults with immunocompromising conditions recommend administration of both PCV13 and PPSV23 vaccines [24, 25]. In pneumococcal vaccine-naïve patients, a dose of PCV13 should be given first, followed by a dose of PPSV23 at least eight weeks later. A booster dose of PPSV23 should be administered five years after the first dose, and a third dose at age 65 years or later, provided that at least five years have elapsed since the last dose of PPSV23.

Among those previously immunized with PPSV23, immunocompromised adults 19 years or older should receive a dose of PCV13 if they have not yet received it, at least one year after receipt of the most recent PPSV23 dose. In patients for whom an additional dose of PPSV23 is indicated, the first PPSV23 dose should be given no sooner than eight weeks after PCV13 and at least five years after the most recent dose of PPSV23 [25].

2 Influenza vaccine

Influenza causes enormous morbidity and mortality among aged and immunocompromised persons.

2.1 Types of vaccine

Vaccines approved for the 2018–19 influenza season include inactivated, recombinant, and live-attenuated influenza vaccines. All three vaccines are available in trivalent or quadrivalent formulations. Live influenza vaccines, like other live vaccines, are contraindicated in SLE patients. [26] .

Because of low immune responses to inactivated influenza virus in immunocompromised patient populations, an ongoing debate pertains to addition of an adjuvant in the vaccine to improve its immunogenicity in SLE and other immunosuppressed patients. Inactivated influenza vaccine licensed in the United States contains no adjuvant, with the exception of Fluad, a trivalent vaccine that contains adjuvant MF59, an oil-in-water emulsion. Adjuvants can enhance immune response and reduce the amount of virus required for immunogenicity of a vaccine [27]. Some studies have concluded that adjuvanted vaccines have comparable safety and immunogenicity to non-adjuvant vaccines, [28] whereas others have reported an association between adjuvanted vaccines and development of a lupus-like disease [29]. A pooled analysis of safety data from 64 clinical trials comparing 20,447 subjects who were immunized with MF59 adjuvant-containing influenza vaccines with 7526 subjects who were immunized with non-adjuvanted vaccine found no significant difference in the incidence of autoimmune diseases between the two groups [30]. A recent meta-analysis of 15 studies showed that the side effects of adjuvanted and non-adjuvanted influenza vaccine in SLE patients were similar to those in healthy controls, but the rate of sero-protection in SLE patients receiving non-adjuvanted vaccines was significantly lower when compared with healthy subjects [31].

2.2 Review of safety and efficacy

The administration of the influenza vaccine in SLE patients has been hotly debated over the past few years, mainly due to concerns that the vaccine may potentiate the onset of SLE or worsen the disease. There are reports of patients developing lupus-like illness, Guillain-Barre syndrome, acute encephalitis or transverse myelitis, and vasculitis, as well as development of anti-phospholipid antibodies after administration of the influenza vaccine [29]. Studies show, however, that influenza infection itself is more likely than influenza immunization to trigger Guillain-Barre syndrome and other autoimmune phenomena [32]. Vaccines can trigger development of auto-antibodies such as ANA and anti-DNA antibodies in SLE patients and in some healthy individuals, without any associated clinically significant illness. In lupus patients who developed high titers of anti-dsDNA antibodies following immunization, the titers returned to baseline by 12 weeks. This suggests that immunization with influenza vaccine is usually innocuous and may lead to increased synthesis of autoantibodies without any associated flare of autoimmune disease [33].

Influenza vaccine was reported in several studies to be well tolerated in patients with SLE. Influenza vaccine immunogenicity appears to be viral strain-specific. In a 2002 study of 24 SLE patients, only 58%, 63%, and 38% responded to the A/Beijing/262/95 (H1N1), A/Sydney/05/97 (H3N2), and B/Harbin/07/94 components, respectively, of the split-virion, inactivated vaccine. These response rates were lower than those seen in the general population [34, 35]. A similar study in 2011 reported lower humoral response to the influenza vaccine in 21 SLE patients when compared to healthy controls [36]. In 2011, the largest prospective study of pandemic non-adjuvanted influenza A (H1N1) vaccine in 1668 patients with autoimmune rheumatic diseases reported good safety outcomes but low antibody responses in 34% of patients who had SLE [37]. Despite these comparatively weak humoral immune responses, influenza immunization can still generate protective immune responses in a majority of SLE patients [28].

A meta-analysis of 18 studies with 1966 SLE subjects and 1112 controls showed that the seroprotection rate was significantly decreased in SLE patients compared to controls after vaccination against A/H1N1 and A/H3N2 vaccination, but not influenza B. Seroconversion rates were significantly decreased in SLE patients after vaccination against A/H1N1 and influenza B, but not A/H3N2. On balance, the influenza vaccine immunogenicity in SLE patients almost reached standard thresholds of protection [38]. Another systematic review and meta-analysis including 17 studies with 1598 SLE patients and 800 healthy controls showed lower immune responses to influenza A strains, whereas immune responses to influenza B were preserved in SLE patients. [39] However, despite comparatively weaker influenza A humoral immune responses, SLE patients did fulfill vaccine immunogenicity criteria, reaching a level considered protective against influenza [28],[38].

2.3 Medication effects:

The effects of immunosuppressive therapies for SLE on vaccine responses are confounders in the studies described above. Nearly all patients in the studies were on drug combinations that make it impossible to determine the influence of specific drugs in modifying the immune responses to influenza vaccines. However, some biologic agents, such as rituximab,

have been shown to impair the immune response [36]. Studies also show that azathioprine can hamper the immune response to the influenza vaccine but that majority of azathioprine-treated patients are still able to mount protective antibody responses [34, 40]. In the BLISS-76 trial, comparing belimumab to placebo for SLE, the belimumab group had essentially preserved titers of pre-existing influenza antibody responses [41].

Recommendation—Inactivated influenza vaccines may have lower seroconversion or seroprotection rates among patients with SLE than healthy controls, but they still offer protection against influenza. Inactivated influenza vaccine is safe and should be administered to all SLE patients annually.

3. _Hepatitis B vaccine

Hepatitis B virus (HBV) is a known cause of acute and chronic hepatitis and cirrhosis. It is also the etiology of approximately half the world's hepatocellular carcinoma. It has infected about 2 billion people worldwide, causing chronic, lifelong infections in more than 350 million [42].

3.1 Type of vaccine

Currently, two single-antigen vaccines and two combination vaccines are licensed in the United States. Both single-antigen vaccines are composed of recombinant hepatitis B surface antigen with aluminium adjuvants(Recombivax and Engerix). The third, Heplisav-B, comprises recombinant hepatitis B surface antigen with a novel immunostimulatory DNA sequence adjuvant known as ISS 1018 which is a synthetic oligodeoxynucleotide containing cytidine-phosphate-guanosine oligodeoxynucleotide (CpG) motifs which act as TLR-9 agonist [43]. Combination vaccines include Pediarix, containing DTaP, HBV, and inactivated polio vaccines, Twinrix, which immunizes against both hepatitis A and HBV, and Comvax which immunizes against Hepatitis B and *Haemophilus influenzae* type b (Hib) [44].

3.2 Review of safety and efficacy

HBV vaccine safety concerns focus primarily on risk of triggering autoimmune conditions. Though the level of evidence is not strong, there are several case reports, case series and retrospective studies describing development of rheumatologic diseases, including SLE, after administration of HBV vaccine [45, 46]. In a murine model study, immunization with HBV vaccine induced acceleration of kidney disease that was manifested by high titers of anti-dsDNA antibodies ($p < 0.01$), early onset of proteinuria ($p < 0.05$), histological damage and deposition of HBs antigen in the kidney. However no human studies have demonstrated similar results [47].

A case-control study based on reports to the vaccine adverse event reporting system (VAERS) revealed a significant increase in the incidence of autoimmune diseases, including SLE, following HBV vaccine when compared to tetanus-vaccinated group [48]. However, no causal relationship between the autoimmune conditions and HBV vaccine has been clearly established [49]; rather, the HBV vaccine was implicated by exclusion of other known causes. An association has been established in genetically susceptible individuals in the right

environmental setting that predisposes them to develop autoimmune disease. In fact, Cooper et al. did not find evidence that HBV vaccine is a risk factor for the development of SLE [50].

In another prospective study of 28 Brazilian SLE patients with inactive disease, HBV vaccine was also determined to be safe and efficacious, with no significant increase in disease flares, anti-dsDNA antibody titers, immunosuppressive medication or steroid requirement over 7 months (from baseline until one month after the third HBV vaccine dose). Protective antibodies developed in 93% (26/28) of patients at the end of the study, which is comparable to the normal adult population response of 90–95%. In addition, the two patients without vaccine responses received an additional fourth dose and developed positive antibody titers to HBV surface antigen without clinical or laboratory flares. These results also suggest that, as in other patient populations, if HBV vaccination did not yield a serologic response after the first three doses, administration of a fourth dose may achieve protective antibody titers [51].

The newly approved Heplisav-B, featuring CpG adjuvant, has proven more immunogenic than the older HBV vaccines in groups with reduced immune function such as the elderly, those who have diabetes and chronic kidney disease, and possibly in persons living with HIV[52–54]. The vaccine has no published experience in SLE patients**.**

3.3 Medication effects

In one study, SLE patients with active disease, immunosuppressive therapy, prednisone doses higher than 20 mg/day and renal failure had impaired immune responses to HBV vaccine [51].

Recommendation—Vaccination against HBV is safe and fully effective in patients with inactive SLE. HBV vaccine response can be impaired in patients with active disease or on higher immunosuppressive doses. ACIP guidelines recommend three doses at 0, 1, and 6 months. Consideration may be given to additional doses of vaccine in patients who fail to respond to the initial series [42]. European League Against Rheumatism (EULAR)guidelines recommend administering HBV vaccine to SLE patients who are or will be at increased risk of infection with risk factors such as living in endemic countries, travel, medical profession or contact with people who have active HBV infection [55]. Heplisav-B is given in a two-dose series over one month, rather than three doses over six months.

4. Diphtheria, pertussis, and tetanus

Diphtheria was a major cause of morbidity and mortality in the early 20th century. Introduction of the diphtheria vaccine led to a precipitous drop in the number of reported cases, with only 5 cases reported in the United States since 2000 [42]. Tetanus toxoid has also made tetanus very uncommon in developed countries, with only 233 cases reported in the United States between 2001 and 2008 [56]. Pertussis continues to cause respiratory morbidity and mortality in infants even in developed countries due in part to the inability of the vaccine to generate a long-lasting immune response. Booster immunizations can help

maintain protection among older children, parents and other contacts of infants, and elderly and immunocompromised persons.

4.1 1Type of vaccine

The three types of vaccines against tetanus, pertussis, and diphtheria are tetanus and diphtheria toxoids (Td); pediatric diphtheria and tetanus toxoids and acellular pertussis aluminium adjuvanted vaccine (DTaP); and adult tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap). Tdap is the most widely used vaccine, licensed for ages 11– 64 years in the United States [57].

4.2 Review of safety and efficacy

In 2013 Csuka et al. reported, in a study of 279 predominantly female patients that serum concentrations of diphtheria antitoxoid IgG and tetanus antitoxoid IgG were comparable between healthy control subjects and SLE patients [58]. In a case series by Battafarano et al, around 90% of SLE patients (65 of 72) immunized with tetanus toxoid achieved a protective antibody response [13], which is very similar to the response rate among the general population [58]. EULAR recommends that SLE patients receive the tetanus toxoid vaccine per the same guidelines as the general population. However, a decrease in immunogenicity with advancing age has been noted in various studies. A study by Older et al. reported few cases of SLE onset following administration of tetanus and diphtheria toxoid; those that occurred followed simultaneous administration of other vaccines [59].

4.3 Medication effects

In general, medications do not interfere with the development of protective antibody titers to diphtheria and tetanus toxoid vaccines. In the BLISS-76 study, belimumab along with concomitant biologic agents (methotrexate, azathioprine or mycophenolate) did not affect preexisting tetanus toxoid antibody titers. In addition, the small number of patients who did receive tetanus vaccine during the study had supratherapeutic titers before and after immunization. This helps to support the case for vaccinating SLE patients against tetanus even when they are require biologics for disease control [41].

Among SLE patients receiving rituximab more than 24 weeks before tetanus vaccination, there was no significant change in humoral immunity response. EULAR recommends passive immunization with tetanus immunoglobulin if urgent tetanus protection is needed within 24 weeks of receiving rituximab [55].

Recommendation—Diphtheria and tetanus toxoid administration appear to be safe and effective in SLE patients. DTaP is the preferred vaccine for children up to 6 years of age. ACIP recommends that a single dose of Tdap should be given: 1) adolescents completing the childhood series between ages 11 and 18 (preferably at age 11 or 12); 2) adults aged 19−–64 years for booster immunization to replace tetanus and diphtheria toxoids vaccine (Td) regardless of the interval since the last dose of Td; 3) adults who have or anticipating to be in close contact with an infant aged <12 months (e.g., parents, grandparents aged <65 years, child-care providers, and healthcare personnel) to reduce the risk for transmitting pertussis [60].

5 *Haemophilus influenzae* type B vaccination

H. influenzae type B (Hib) was an important cause of epiglottitis, pneumonia, arthritis, meningitis, and cellulitis until adoption of the Hib vaccine in the 1980s.

5.1 Type of vaccine

Food and Drug Administration (FDA) has approved three monovalent polysaccharide-protein conjugate aluminium adjuvanted vaccines and three combination vaccines against Hib. The combination vaccines could include HBV vaccine, DTaP and inactivated polio vaccine, or meningococcal vaccine, respectively [61].

5.2 Review of safety and efficacy

In a study by Battafarano, Hib conjugate vaccine achieved a protective antibody response in 64 of 73 SLE patients (88%). The vaccine was well tolerated and had no effect on SLE disease activity [13]. According to the local vaccination guidelines for autoimmune diseases from Switzerland and Portugal, the Hib vaccination was recommended when patients' disease was in a stable state [62, 63].

5.3 Medication effects

Studies have shown decreased antibody response to Hib vaccine in patients taking cyclophosphamide, prednisone, azathioprine either alone or in combination [13]. Immunizing proactively in a disease-stable state obviates the need to vaccinate in a reduced immune state, and eliminates confusion between symptoms of a disease flare and vaccine side effects [62].

Recommendation—Hib vaccine is well tolerated and effective in patients with SLE who are in disease stable states. CDC recommends Hib conjugate vaccine be given to children as part of the standard childhood vaccination schedule, and to unimmunized adults who are asplenic and all adults following stem cell transplantation. [61].

6. Rabies vaccine

Postexposure vaccination and passive immunization against rabies are important because of the virtually 100% mortality rate of untreated rabies infection.

6.1 Types of vaccine

Three inactivated rabies vaccines are manufactured, including human diploid cell vaccine (HDCV), rabies vaccine adsorbed (RVA), and purified chick embryo cell vaccine (PCECV). Of those, only HDCV and PCEV are available for use in United States [64]. Postexposure vaccine is administered in a five-dose or reduced four-dose regimen, along with rabies immune globulin. Only the five-dose schedule is recommended for immunocompromised persons.

6.2 Review of safety and efficacy

There are no studies evaluating the safety and immunogenicity of rabies vaccination in the SLE patient population.

6.3 Medication effects

Immune response to the vaccine could be blunted with the use of DMARDs such as chloroquine (dose 250–500mg particularly (HDCV) or immunosuppressive medications including corticosteroids [65]. Therefore, nonessential immunosuppressive agents should be avoided during rabies postexposure prophylaxis.

Immunosuppressed patients should avoid activities involving wildlife that require pre-exposure rabies prophylaxis. If avoiding exposures is not possible, ACIP recommends that patients receive intra-muscular pre-exposure vaccine. [64].

Recommendation—Immune response may be blunted in patients who are taking immunosuppressive medication during pre-exposure and post-exposure prophylaxis. SLE patients should receive the full five-dose postexposure vaccination schedule, minimizing the use of immunosuppressive medications during the vaccine series. SLE patients who receive rabies pre-exposure or postexposure prophylaxis should have rabies antibody titers checked upon completing the vaccine series [66].

7. Human papilloma virus (HPV) vaccine

HPV is the most common sexually transmitted disease in the world, newly affecting approximately 14 million people each year [67]. HPV causes genital warts and malignancy including cervical, penile, anogenital cancers, as well as oropharyngeal cancers.

7.1 Types

Currently, three HPV vaccines are available: the quadrivalent (qHPV), the bivalent (bHPV), and the 9-valent (9vHPV) vaccine. All contain aluminium-based adjuvants to enhance immune response. The qHPV is the first vaccine to protect against high-risk HPV serotypes (6, 11, 16, and 18), which are associated with most genital warts and cervical cancer. It is licensed for use in both females and males aged 9 through 26. Bivalent vaccine targets HPV serotypes 16 and 18, and is licensed for use in females age nine through 25 [67]. The newer 9-valent HPV virus-like particle (VLP) vaccine targets five oncogenic serotypes (31, 33, 45, 52, 58) in addition to the four high- risk HPV serotypes (6, 11, 16, and 18), thus improving cervical cancer prevention from approximately 70% to 90% and preventing 85%–95% of HPV-related vulvar, vaginal, and anal cancers [68–72].

7.2 Review of safety and efficacy

Reports in the literature describe new-onset SLE, lupus-like syndromes, and exacerbations of underlying autoimmune disease following HPV vaccine administration [73, 74]. However, most of these patients had personal or family history of autoimmune diseases, making them more genetically susceptible to autoimmunity [75, 76]. A case-control study based on reports to the VAERS database from 2006 to 2014 included 28 reports of SLE

developing among female HPV vaccine recipients and an odds ratio of 7.626 (95% CI 3.385–19.366) for development of SLE following administration of quadrivalent HPV vaccine [77, 78]. The association may be confounded by overlap in the age range of patients receiving HPV vaccination and the age at which initial lupus manifestations typically develop. An analysis of quadrivalent HPV vaccine safety combining 15 studies in more than a million preadolescent, adolescent, and adult recipients from various countries did not find autoimmune diseases as an adverse event following HPV administration. The vaccine was generally well tolerated by SLE patients [79].

Grimaldi-Bensouda et al. found no increase in the risk of developing SLE following vaccination with the quadrivalent vaccine within the 4-year study period in a case-control study including patients aged 14–26 years from 113 specialized centers [80]. Prospective studies have also shown that the vaccine is safe and well tolerated in adolescents and young women with SLE, with no increase in disease activity and development of a seropositivity rate ~80–90% for HPV serotypes 6, 11, 16, and 18 [81, 82]. A study by Heijstek et al. compared six SLE patients with 49 healthy controls; all subjects became seropositive after the third dose of vaccine for both HPV 16 and 18; however, SLE patients had lower antibody titers for these serotypes than healthy controls [83]. Reviewing National Hospital Discharge Survey, National Inpatient Sample and Kids Inpatient Sample Database, no records indicated increasing hospitalizations or emergency admissions from lupus in persons who received HPV vaccines [84].

VAERS database has demonstrated an association of Postural Orthostatic Tachycardia Syndrome (POTS) with HPV vaccination [85–87]. The etiology of POTS remains largely unknown, however studies have suggested that a small number of patients suffer from small-fiber neuropathy leading to autonomic dysfunction [88, 89]. The evidence of an association with immunization has been inferred from questionnaire-based case series or individual case reports; study methodology failed to include skin biopsies that might have demonstrating small fiber neuropathy. Although vaccine adjuvant was postulated as the trigger, some have argued that was unlikely as the adjuvant content is small and could be easily excreted [90, 91] .

An association between HPV infection itself and increased incidence of SLE was reported, leading to conjecture that the virus may trigger SLE through molecular mimicry [89]. However, SLE patients have higher rates of developing abnormal pap smears and precancerous cervical intraepithelial lesions than healthy women or those who have other autoimmune diseases [84, 92, 93]. The dysregulation of innate and adaptive immune responses in SLE patients impairs the clearance of virus, resulting in persistent carriage of HPV. Long term infection combined with the higher prevalence of multiple HPV types in SLE patients, including high-risk subtypes, predisposes them to cervical dysplasia [94–97]. Until recently, cervical cancer incidence was thought to be equivalent in SLE and healthy populations despite an increased frequency of premalignant lesions among SLE patients [94, 98]. However, a recent systemic review of 27 studies noted an increased rate of cervical cancer in SLE patients [93]. A hospital-based cohort of 576 SLE patients linked to the Danish Cancer Registry also found high incidence of HPV-associated tumors [99]. Prevalence of anogenital warts was found to be lower than that of cervical dysplasia [100],

however, when present, they are often large and recalcitrant to treatment, requiring surgical debulking [101, 102].

7.3 Medication effects

Studies have shown lower immunogenicity of HPV vaccine with lower seroconversion rates in patients taking prednisolone and mycophenolate mofetil [81]. Vaccine administration can influence seroconversion rates with certain HPV types in SLE patients on immunosuppressive medications. Mok et al. have shown lower seroconversion rates of 74 % and 75% that were noted in HPV 6 and HPV 18 after 7 months [82], though patients in that study were older than the optimal age for immunization.

Incongruity exists among different studies in regard to the influence of immunosuppressive agents on cervical dysplasia. The majority found no association between immunosuppressive drugs and increased frequency of cervical dysplasia, while a few studies pointed to the development of cervical dysplasia following cyclophosphamide exposure [103, 104].

Recommendations

HPV vaccines have proven safe and immunogenic in patients with SLE. ACIP recommends routine HPV vaccination be initiated at age 11 or 12 years, but can be started as early as age 9 years. Vaccination is also recommended for females aged 13 through 26 years and for males aged 13 through 21 years (and immunocompromised males through age 26) who have not completed the 3-dose series. Vaccination of females is recommended with 2v HPV, 4v HPV, or 9v HPV. Vaccination of males is recommended with 4v HPV or 9v HPV. Given the elevated risks associated with HPV infection in SLE patients, immunization of this population should be strongly encouraged [68].

8. Live -attenuated vaccines

Live-attenuated vaccine usage in immunocompromised patients impends the risk of uncontrolled viral replication. Therefore, their use is generally contraindicated in these patient populations. These include live-attenuated influenza vaccine (FluMist), chickenpox and herpes zoster vaccines, measles, mumps and rubella vaccine, oral polio vaccine, oral typhoid vaccine, and yellow fever vaccine.

Herpes zoster vaccine

VZV reactivation is debilitating in SLE patients. Decreased cell-mediated immunity from disease itself or immunosuppressive medications predisposes this patient population to the development of dermatomal or disseminated herpes zoster (shingles).

Types—The live-attenuated herpes zoster vaccine (Zostavax) contains the Oka strain of VZV. Its potency is at least 14 times that of the varicella vaccine, which uses the same VZV strain [105]. The vaccine is licensed in the United States for adults >50 years of age; however, CDC recommends its use for patients > 60 years for optimal cost effectiveness [105, 106]. A new recombinant subunit vaccine (Shingrix) using VZV glycoprotein E and

adjuvant $AS01_B$ was recently approved in 2017 for use in patients age 50 years and over, and is under clinical investigation for use in immunocompromised patients [107–109].

Review of safety and efficacy—Live-attenuated VZV vaccine can be dangerous for immunocompromised patients because of its ability to cause serious infection with the vaccine strain of VZV in the presence of reduced cell-mediated immunity [110–113]. In addition, VZV-naive persons are at risk of acquiring vaccine-strain VZV infection after exposure to a recent live-attenuated VZV vaccine recipient who has a vaccine-related rash [114].

A retrospective observational study by Zhang et al demonstrated that administration of live-attenuated VZV vaccine to patients with rheumatoid arthritis, psoriasis, psoriatic arthritis, and ankylosing spondylitis who were receiving biologics agents and DMARDs, despite published recommendations to the contrary [REF 117], was not associated with a short-term increase in incidence of herpes zoster [115]. A prospective pilot study among 10 SLE patients in Oklahoma showed that live-attenuated VZV vaccine was safe and immunogenic in this small cohort. However, small sample size and inclusion of patients on milder immunosuppressants, such as hydroxychloroquine and low-dose prednisone (mean daily dose ~ 7 mg) and methotrexate are the major limitations of the study [116]. A case-control study of severe autoimmune adverse events found no increased risk of SLE after live-attenuated VZV vaccination [117].

Leroux-Roels et al. have shown that the adjuvant gE subunit vaccine, Shingrix, was well tolerated and more immunogenic than live-attenuated VZV vaccine in younger (18–30 years) and older (50–70 years) immunocompetent adults [118]. The subunit vaccine is an attractive alternative to the live-attenuated vaccine given its ability to elicit a stronger immune response and greater reduction in the risk of herpes zoster and post-herpetic neuralgia in elderly individuals, without risk of vaccine-related infection [107, 119, 120]. The recombinant vaccine has not yet been studied systematically in many immunosuppressed populations, but has proven safe and immunogenic among stem cell transplant recipients and HIV- infected persons [108] [109]. Although no published studies have yet described its use among patients with autoimmune disease, the rheumatology community eagerly awaits studies to determine whether the subunit vaccine will make it possible to protect this patient population safely.

Recommendations: As per current ACIP guidelines, live-attenuated VZV vaccine can be given to the patients on methotrexate (<0.4 mg/Kg/week), azathioprine (<3.0 mg/Kg/day), 6-mercaptopurine (<1.5 mg/Kg/day), or prednisone: low-to-moderate dose (<20 mg/day or short-term corticosteroid therapy (<14 days) [121]. However, there is a lack of published data to support the safety of live-attenuated VZV vaccine in SLE patients on moderate to high doses of immunosuppressive medications. Live-attenuated VZV vaccine should be administered at least 2 weeks, and ideally 4 weeks, before initiation of immunosuppressive therapy [121]. In practical terms, SLE patients with more severe manifestations will not be able to receive live-attenuated VZV vaccines due to their need for continuous immune suppression.

The CDC recommends that healthy adults 50 years and older receive two doses of Shingrix, 2 to 6 months apart [122]. There are no guidelines for immunosuppressed individuals at this time.

Polio Vaccine

Poliovirus is highly infectious, with seroconversion rates of greater than 90% among susceptible household contacts of infected persons. Although nearly eradicated in most of the world, wildtype poliovirus persists in limited regions where universal vaccination remains challenging.

Types—Two types of polio vaccine are available worldwide: live-attenuated oral polio vaccine (OPV) and inactivated polio vaccine (IPV). IPV is safer, but has lower immunogenicity and efficacy, and must be injected. OPV is associated with vaccine-associated paralytic poliomyelitis, particularly in adults and immunocompromised children [123]. Use of oral polio vaccine was discontinued in the United States in 2000 [42] but continues to be used throughout much of the developing world because of effectiveness in eliminating widtype virus and ease of administration in public health campaigns [REF 121].

Review of safety and efficacy—A retrospective study among vaccinees following a nationwide immunization campaign in Israel found 73 recipients to have SLE, among whom 5% (4/73) developed disease flares after receipt of oral (1/24) or inactivated (3/49) vaccine [124].

Recommendation: In the United States, IPV is administered to children as part of routine childhood immunization between 2 months and 6 years of age. Adults are generally not immunized unless they plan to travel to polio-endemic areas. The WHO recommends childhood immunization with OPV in areas where wildtype poliovirus continues to circulate [125].

Measles-mumps-rubella (MMR) vaccine

Measles, mumps, and rubella are febrile viral infections that can cause severe disease with serious complications that make their prevention a public health imperative. Mumps can cause meningitis, encephalitis, and orchitis. Measles causes encephalitis and pneumonia, which is the major fatal complication. Rubella causes miscarriages and devastating birth defects.

Types—Single-antigen measles, mumps, and rubella vaccines are not offered in the United States. The two combination vaccines are measles-mumps-rubella (MMR) and measles-mumps-rubella-varicella (MMRV). Measles immune globulin is available for postexposure prophylaxis of pregnant women, babies, and immunosuppressed persons who are exposed to measles [126].

Review of safety and efficacy—There are limited studies on the use of MMR in the SLE patient population, as this vaccine is usually given early in life before the onset of SLE.

In a study of 30 pediatric SLE patients with active and inactive disease, measles antibody titers were similar to those of healthy controls [127].

Recommendation: Immunocompromised individuals should not receive the live-attenuated MMR or MMRV vaccine. Transmission of attenuated measles, mumps, and rubella vaccine strains from immunized individuals has not been reported (except rarely via breast milk); hence, close contacts of immunocompromised persons, including healthcare providers, may receive the MMR vaccine. Close, nonimmune contacts of immunocompromised persons should be immunized with the MMR vaccine in an effort to protect the vulnerable patient [126].

Other live vaccines: As reported by Milet et al. [1] there are no published guidelines for lupus patients, but 2002 British Society of Rheumatology practice guidelines [NEED REF FOR THIS] and the 1993 recommendations of the ACIP [128] recommend waiting at least four weeks before initiating immunosuppressive therapy following live vaccine administration. As with live-attenuated VZV vaccine, a prednisone dose of at least 20 mg/day for more than two weeks is considered to be immunosuppressive.

Other vaccines: There are no specific data available to date on hepatitis A, pertussis, or meningococcal vaccination in patients with SLE.

Barriers to vaccination in SLE: The growing body of literature on immunization of patients with autoimmune disease supports their timely immunization against vaccine-preventable diseases; however, there are several barriers that may prevent patients from being properly immunized [129].

Failure to recommend vaccination—Errors of omission on the part of providers are perceived as one of the common barriers. Lawson et al. have shown that oversights and failure to address patient concerns are the most frequent reasons why SLE patients do not receive pneumococcal and seasonal influenza vaccines. The study suggested that increasing vaccination rates in SLE requires improved processes at the provider level through incorporation of measures like preventive care checklists and taking responsibility for relaying necessary information. The electronic medical record may be a useful tool for issuing reminders or alerts for vaccination as well as improving communication between primary care and specialty providers [130]. A quality improvement project at the Children's Hospital of Wisconsin rheumatology clinic used simple measures such as the development of an immunization algorithm, pre-visit planning for vaccination, and placing vaccine reminders on clinic forms that significantly improved the rates of pneumococcal vaccination from 6.7% to 48.4% for PCV13, 8.9% to 28.4% for PPSV23, and 0 to 23% for combined PCV13 and PPSV23 [131].

Communication Barriers: Communication challenges among both providers and patients can serve as another important barrier. A survey of 301 primary care physicians exploring suboptimal HPV vaccination rates showed that only 67% of providers gave the vaccine. Discomfort with discussing HPV vaccination with early adolescent girls (OR 5.10) or their mothers significantly contributed to the low rate of vaccination [132]. Another study of HPV

vaccine administration identified three main communication barriers: reluctance of parents and patients to discuss HPV vaccination, limited awareness among patients, and inadequate patient access to health care. Specific discussions initiated and sustained by providers to encourage completion of the vaccine series at the recommended age of 11–12 years were identified as a potential approach to improve vaccination rates [133].

Perceived risk of autoimmune reactions/ Adjuvant related autoimmune syndrome (ASIA): Other barriers to immunization include fear of triggering autoimmune reactions or syndromes in response to vaccination. Weak evidence, limited primarily to case series and observational studies, suggests an association between autoimmunity and vaccination, but there is no convincing evidence to support this highly controversial link. There are many suggested mechanisms for development of autoimmunity after immunization: (a) adjuvant-related autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome); (b) antigen-specific (molecular mimicry) or nonspecific (bystander activation) autoimmune reaction; (c) autoimmunity activated by preservatives or other vaccine components [134, 135].

ASIA syndrome, first described by Shoenfeld et al. in 2011, is a constellation of symptoms triggered by adjuvants. Adjuvant was postulated to be an environmental immune trigger resulting in immune dysregulation causing autoimmune and auto-inflammatory disease in a genetically susceptible host [29]. To date more than 300 suspected ASIA syndrome cases have been reported worldwide [136]. Physicians have been remained skeptical of ASIA syndrome, considering these reports to be lacking in scientific evidence. Segal et al have clarified and validated the concept of ASIA, noting that identification of ASIA is not meant to blame vaccines for autoimmunity, but rather to address the role of environmental adjuvants as a whole in the induction of autoimmunity among populations at risk [137]. The authors note that genetic predisposition plays a major role in the development of autoimmunity that may occur as an adverse reaction to vaccination. For example, Mitchell et al have shown a higher frequency of DR2 and DR5 in rubella vaccine recipients with arthropathy [138]. Segal et al have suggested developing vaccines containing unique viral peptides that lack homology to the human proteome and thus potentially avoid vaccine-induced molecular mimicry and autoimmunity [137].

Alum or aluminium is the most commonly used adjuvant to enhance the immunogenicity of a vaccine. Studies examining exposure to aluminium including infants found that vaccinations do not raise aluminium levels to even the minimal risk levels [139–141]. The FDA limits the elemental aluminium content of a single vaccine injection to 0.85 mg, a value equivalent to 2.45 mg Al(OH)3 per dose [142, 143]. More aluminium is consumed through dietary intake in the form of fruits and vegetables, beer and wine, seasonings, flour, cereals, nuts, dairy products, baby formulas, antacids that result in a much higher daily oral dose of 8–9 g, which has also been deemed safe. The dietary dose needed for toxicity is vastly greater than that delivered through vaccination [144, 145].

At the same time, recent trials have reported a diminished or limited immunogenic role for Al(OH)3 adjuvant in certain vaccines [146–148]. Depending on the vaccine and dose, influenza vaccines with alum adjuvant were no more effective toward inducing an immune

response than influenza vaccines without adjuvant [149, 150]. There were no differences in the frequency of new cases of autoimmune disease at any age. One potential area for future research is development of adjuvant-free vaccines that are nonetheless sufficiently immunogenic to confer protection, in order to overcome the controversy associated with adjuvant usage.

Recrudescence of serious infections have been seen when enough people opt out of routine immunizations. Japan, where health records are easily tracked, has high rates of vaccine-preventable diseases relative to other developed countries, in stark contrast to the country's other positive health indicators [151]. Decades of vaccine reluctance has caused reemergency of pertussis and measles [152, 153]. More recently, national guidelines suspended active recommendation to administer HPV vaccine to girls based on media-reported adverse events attributed to the vaccine, including pain and motor disability. Although a Japanese murine model of HPV vaccine-associated neuro-immunopathic syndrome (HANS) has been described [154], the association should be interpreted with caution as there are no human studies demonstrating the same.

Vaccines, like any other medication or medical intervention, can certainly have adverse effects. Some rare but important side effects may not be detected during clinical trials, and are only noted in post-marketing surveillance for adverse events. For example, Rotashield, the first live-attenuated rotavirus vaccine, was licensed in August 1998 but had to be withdrawn in October 1999 due to cases of intussusception occurring within 3 to 8 days of vaccine administration [155, 156]. Another example was LYMErix vaccine, approved by the FDA in 1998 and withdrawn from the market in 2002 following reports of autoimmune arthritis in HLA- DR patients [157, 158] . These events should be interpreted as vital red flags in the invaluable practice of immunization, alerting practitioners to the need for constant vigilance, but not changing the underlying fact that vaccines are the only means for achieving widespread protection against potentially lethal infections.

Conclusion

Vaccinations are the most important contributions in the history of medicine for public health. They have enabled the elimination or control of many serious and life-threatening infectious diseases worldwide over the past 200 years. There are clear benefits to vaccination in patients with SLE, and, overall, inactivated vaccines appear to be safe. Further rigorous studies are needed on the safety and efficacy of vaccines given to patients with SLE who are on immunosuppressive medications. Physicians should discuss and educate patients about the risks and benefits of vaccination as part of their routine care of SLE patients.

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Table 1.

Inactivated vaccines

VACCINE TYPE	INDICATION	REPEAT VACCINATION	SPECIAL CONSIDERATION	SAFETY CONCERNS
PNEUMOCOCCAL VACCINE	All previously un-immunized patients.	A dose of PPSV 23 should be repeated in 5 years.	PPSV-23 should be administered atleast 8 weeks following PCV −13.	Well tolerated. Conjugate (PCV −13) vaccine not tested in SLE patients.
INFLUENZA VACCINE	Yearly during Flu season.	No data. Patients generally develop lower antibody response. May have inadequate protection.	None	May develop auto-antibodies, with no clinical significance.
HEPATITIS B	All previously unimmunized patients. Patients with risk factors like household contacts, health care worker, IV drug use, multiple sexual partners.	Check titers every year after initial series is completed. Booster vaccination to be given for low titers.	Additional dose after one month of complete series if there is inadequate antibody response.	No evidence for increased disease activity.
DIPTHERIA AND TETNUS TOXOID	19–64 years – single dose of Tdap as booster of last dose of Td>10 years	Booster for protection against pertsussis if interval is shorter than 10 yrs since last Td	Consider booster in patients with skin laceration/ soiled wounds. Adults <65 years should receive a single dose of Tdap if anticipating contact with infant < 12 months of age	No evidence for increased disease activity.
HAEMOPHILIS INFLUENZAE TYPE B	All previously un-immunized patients	No data.	None	No evidence for increased disease activity.
RABIES VACCINE	Pre and post exposure prophylaxis	Check titers to ensure adequate response if patient is on chloroquine, steroids or other immunosuppressive	Avoid activities requiring pre-exposure prophylaxis.	No evidence of increased disease activity
HPV VACCINE	All previously unimmunized individuals starting around 11–12 years of age (earliest at 9)through 21 for males and 26 for females	Good seroconversion rate. No need for booster.	None	No evidence of increased disease activity

Table 2.

Live Vaccine

VACCINE TYPE	INDICATION	REPEAT VACCINATION	SPECIAL CONSIDERATION	SAFETY CONCERNS
HERPES ZOSTER VACCINE	All previously unimmunized individuals. Await for at least 4 weeks before starting immunosuppressive treatment.*	Not indicated	May consider using new adjuvant recombinant vaccine as an alternative.	Limited studies published. No evidence of increased disease activity based on current evidence.
MEASLES-MUMPS-RUBELLA	Contra-indicated in patients on high doses of immunosuppressive medications.	Not indicated	Post-exposure therapy after exposure to Measles regardless of prior immunization status	No safety data is available
POLIO VACCINE	Unvaccinated immunocompromised adults should receive enhanced inactivated polio vaccine (eIPV)	Not indicated	Household contacts should receive enhanced inactivated polio vaccine (eIPV)	Patient may experience disease flare after inactivated or oral polio vaccine.

*Current ACIP guidelines, allows Zostavax while patients are on Methotrexate (<0.4 mg/Kg/week), Azathioprine (<3.0 mg/Kg/day), or 6-mercaptopurine (<1.5 mg/Kg/day) or Prednisone: (<20 mg/day or <14 days).

Table 3.

Key Points

1. SLE patients similar to other patients with autoimmune diseases continue to be are under-vaccinated against common infections.
2. Inactivated vaccine in general appear to be safe.
3. Live vaccines (if possible) should be given at least 4 weeks prior to starting immunosuppressive therapy.
4. Studies are needed in SLE patients to determine safety and efficacy of vaccines against commonly occurring pathogens such as Herpes Zoster.
5. Physician and patient education is needed to overcome the barriers against vaccination in SLE patients.