REVIEW ARTICLE

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Efficacy and Safety of Vaccinations in Systemic Lupus Erythematosus

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ABSTRACT

Patients with rheumatological or immunological conditions, such as systemic lupus erythematosus (SLE), are particularly vulnerable to infections either due to the underlying immunological aberrations of the disease itself or treatment-related/iatrogenic immunosuppression. Infections remain the leading cause of morbidity and mortality in SLE patients and appropriate vaccination is of paramount importance. Despite clear guidance for the most common vaccinations, the greatest barrier to appropriate vaccinations likely remains with physician awareness or willingness for recommendation. To address this, we review the current evidence regarding the impact of the most commonly recommended vaccinations on SLE.

***Keywords*:** Human Papilloma Virus; Immunization; Influenza; Pneumococcal; Systemic Lupus Erythematosus; Vaccination; Zoster.

INTRODUCTION

Vaccination is often regarded as the greatest achievements of modern medicine and prevents two to three million infection-related deaths annually [1]. Patients with rheumatological or immunological conditions, such as systemic lupus erythematosus (SLE), are particularly vulnerable to infections either due to the underlying immunological aberrations of the disease itself or treatment-related/iatrogenic immunosuppression. Infections remain the leading cause of morbidity and mortality in SLE patients [2]. Vaccinations for rheumatology patients are therefore especially important and clear recommendations are available [3–5].

Infection remains a leading cause of morbidity and mortality for lupus patients, accounting for around 25% of deaths [2,6–8]. The most frequently reported infections in SLE patients are bacterial; especially respiratory, urinary tract and soft tissue infections [8]. Most infections are caused by common pathogens, such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli* and *Pseudomonas aeruginosa* [6]. While some of the most common reported viral infections include influenza, herpes zoster and human papillomavirus (HPV) [7]. Therefore, immunization against such common pathogens would be of immense benefit.

Despite this, the greatest barrier of vaccinations in SLE patients is physicians failing to recommend them [9]. Previous studies have shown that only around half of SLE patients received indicated influenza and pneumococcus vaccinations [10]. Suboptimal coverage is likely secondary to lack of physician awareness or concerns regarding vaccination efficacy and/or risks on lupus flare. To address this, we review the current evidence regarding the impact of the most commonly recommended vaccinations on SLE.

INFLUENZA VACCINATION

It is estimated that over 400,000 influenza-associated respiratory deaths occur annually, accounting for 13% of all global health estimates respiratory infection deaths [11]. The influenza vaccination is composed of inactivated influenza A and one influenza B viruses and confers protection by induction of virus-neutralizing antibodies mainly against viral hemagglutinin. Both

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inactivated and live attenuated formulations are available, although the live attenuated formulation has not been recommended for the 2016–2017 and 2017–2018 influenza seasons [12]. Influenza vaccination in SLE patients is associated with lower morbidities, hospitalization rates as well as mortality risk [13]. The efficacy and safety of the influenza vaccination have been long demonstrated in SLE patients and recommended by the European League Against Rheumatism (EULAR) [3–5,14–16].

Despite conflicting reports in the past, a recent systematic review and meta-analysis concluded that there is no significant difference in seroprotection or adverse event rates between SLE patients and healthy controls [17]. Although the vaccine has been reported to transiently trigger generation of autoantibodies, it does not induce clinical flares of SLE [18,19]. Moreover, contrary to previous belief, it has also been suggested that SLE patients may conversely develop improved immune response after influenza vaccinations, generating anti-influenza antibodies with higher binding activities and neutralization capacities [20].

For the 2019–2020 season, the Centre of Health Protection (CHP) recommends the seasonal influenza vaccination to all members of the public except those with known contraindications [21]. We therefore recommend that all SLE patients should be encouraged to receive the seasonal inactivated influenza vaccination annually. The live attenuated influenza vaccines should be avoided as it is contraindicated in immunocompromised patients due to the potential for transmission of the vaccine viruses.

PNEUMOCOCCAL VACCINATION

S. pneumoniae is the most common cause of severe community-acquired pneumonia and leads to an estimated 1.6 million deaths annually [22,23]. SLE patients have high susceptibility for invasive pneumococcal infections, with more severe and frequent rate of invasive infections, as well as higher need for intensive care admissions [24,25].

Two types of pneumococcal vaccines are available, namely the Pneumococcal polysaccharide vaccine (PPSV) and Pneumococcal conjugate vaccine (PCV). The 23-valent PPSV was developed to include 23 purified free capsular polysaccharide antigens, which represents around 60%–70% of cases of invasive pneumococcal disease in the United States [26]. The PCV was developed to address the problem of low immunogenicity of PPSV in children below the age of 2 years. Conjugated vaccines are polysaccharides conjugated to an immunogenic protein and can stimulate a T-cell dependent response. This therefore elicits a serotype-specific memory B cell response, which may theoretically induce a greater functional immune response than PPSV (for the serotypes covered) [27]. There have been concerns that repeated vaccination with PPSV may lead to hyporesponsiveness and currently a "prime-and-boost" strategy with the administration of PCV followed by PPSV (at least 8 weeks later) is recommended [28,29].

Despite past controversies, systematic review and meta-analysis demonstrated that the immunogenicity of pneumococcal vaccination is preserved in SLE patients (compared to healthy controls) and was not associated with changes in disease activity scores [19]. Unlike the influenza vaccination, the PPSV does not induce the generation of autoantibodies [30]. There was also no immunological effect (in terms of lupus serology or disease flare), after pneumococcal vaccination [31].

Nowadays, the PCV and PPSV only exist as 13-valent (PCV13) and 23-valent (PPSV23) vaccinations, respectively. The Hong Kong CHP recommends high-risk individuals (which specifically include immunocompromised states) aged 2 years or above to receive a single dose of PCV13, followed by a single dose of PPSV23 1 year later [32]. Vaccination with just PPSV23 only is no longer recommended. These recommendations are similar to the United States' Center for Disease Control (CDC) and Advisory Committee on Immunization Practices (ACIP) guidelines for adults with immunocompromising conditions, although they instead recommend a time interval of "at least 8 weeks," and a booster dose of PPSV23 5 years after the first dose, and a third dose at age 65 years or later [33]. Despite the lack of large prospective lupus-specific studies, the pneumococcal vaccine is safe and efficacious in SLE patients and routine vaccination (with a single dose of PCV13 followed by a dose of PPSV23 at least 8 weeks later) should be recommended. We recommend the same recommendations as the ACIP guidelines in regard to administrating a single dose of PCV13, followed by a dose of PPSV23 at least 8 weeks later for vaccine-naïve patients. Patients who had received PPSV23 previously (but never PCV) should be given PCV13 at least 1 year after their last PPSV23, and a PPSV23 booster thereafter (at least 8 weeks after PCV13 and 5 years after the most recent PPSV23).

HPV VACCINATION

HPV is a DNA virus from the papillomavirus family and is the most commonly sexually transmitted infection worldwide. Depending on the genotype, HPV can cause a variety of benign conditions (such as anogenital warts), to premalignant or malignant cervical abnormalities. High-risk HPV genotypes (especially types 16 and 18) are particularly oncogenic and strongly associated with development of cervical cancer [34]. HPV infections are usually spontaneously cleared via cell-mediated immunity without any treatment, but this process seems to be impaired in SLE patients [35,36]. Meta-analysis and systematic review found that SLE patients are at higher risk for HPV infection and cervical dysplasia than the general population [37,38]. This may be secondary to predisposition to more persistent high-risk and multiple HPV infections [36]. This suggests that patients with SLE may especially benefit from prophylactic HPV vaccination.

Various formulations of HPV vaccinations, varying in the number of HPV types, are available to prevent initial HPV infection and subsequent HPV-associated lesions. All formulations contain both types 16 and 18, which account for around 70% of all cervical cancers. The quadrivalent HPV vaccine has been shown to be efficacious in reducing HPV-related disease or infection [39,40]. HPV vaccination may also help to reduce incidence of anogenital warts as well as certain head and neck cancers [41]. However, HPV vaccination cannot offer a complete 100% protection and cervical cancer screening should always be advocated as secondary prevention of cervical cancer. Previous reports of a possible association of thromboembolic events and the quadrivalent vaccine were disproven by subsequent large multi-nationwide studies [42]. There had also been some reports describing new-onset SLE following HPV vaccinations, however no association was found after a combined analysis of more than 1 million HPV vaccine recipients between 2006 and 2015 [43]. HPV vaccinations have been proven to be safe and immunogenic in women with SLE, with no increase in disease flare after vaccination or induction of autoantibodies [44–46].

The 9-valent HPV vaccination is now included in the Hong Kong Childhood Immunization Programme for girls of suitable ages [47]. Given the increased risk of HPV infection and its complications, HPV vaccination should be recommended for women with SLE before sexual debut as per local guidance. Although routine vaccinations for male patients have been recommended in many countries, the bulk of evidence regarding HPV vaccination has been from female patients (including SLE). In Hong Kong, HPV vaccination is licensed for males but still is not routinely recommended due to limited experience and studies on cost-effectiveness [47].

HERPES ZOSTER VACCINATION

Varicella-zoster virus infection can lead to either varicella (chickenpox) or herpes zoster (shingles). Clinical resolution of the primary varicella infection leads to establishment of a latent infection within the cranial or spinal ganglia, with subsequent viral reactivation leading to herpes zoster [48]. Approximately, one in three persons will develop zoster during their lifetime, with an estimated 1 million episodes in the United States annually [49]. Postherpetic neuralgia and bacterial superinfections and led to significant burden of disease morbidity and even mortality. The incidence of zoster increases with age, presumably due to the accompanying decline in virus-specific cell-mediated immunity [50]. Likewise, immunocompromised hosts, such as SLE patients, are at increased risk of zoster reactivation, which may even be fatal [51,52]. Use of immunosuppressive therapies for SLE, such as prednisolone and mycophenolate mofetil, also confers additional risk of zoster reactivation [52].

Two zoster vaccinations are available — a live attenuated zoster vaccine and an inactivated recombinant vaccine. The CDC recommends the live attenuated zoster vaccine for patients >60 years, and the vaccine is licensed for adults >50 years [53]. There only are recommendations for the varicella (chickenpox) vaccine in childhood but no local guidance regarding zoster vaccination in Hong Kong. Although live vaccines are generally avoided in immunosuppressed patients, the live attenuated zoster vaccine can be administered to those receiving only low-dose immunosuppression, including low-dose steroid (equivalent to prednisolone <2 mg/kg, with maximum ≤20 mg/day), methotrexate ≤0.4 mg/kg/week, azathioprine ≤3 mg/kg/day or 6-mercaptopurine ≤1.5 mg/kg/day [54]. A local randomized controlled trial showed that the live attenuated zoster vaccine was well-tolerated and immunogenic in patients with stable lupus not receiving intensive immunosuppression [55]. The EULAR guidelines suggest that the zoster vaccination may be considered on a case-by-case basis. If possible, the vaccine should be given at least 4 weeks

before starting immunosuppressive therapies. A careful risk assessment should be taken, including ascertaining a history of primary varicella infection (or serological evidence of previous varicella infection), prior episode(s) of zoster and evaluating the patient's overall immunocompromised state (both disease and treatment related) as well as if temporary discontinuation of immunosuppression may be necessary or feasible. Patients should be adequately counseled on the risk of infection with the vaccine strain of zoster. The inactivated recombinant vaccine is not contraindicated in immunocompromised patients, but still not yet available in many countries including Hong Kong. It has also not been studied in many immunosuppressed populations, including lupus patients.

OTHER ROUTINE VACCINATIONS IN THE HONG KONG

Other vaccinations recommended in the Hong Kong Childhood Immunization Programme include the Bacilli Calmette–Guerin (BCG), hepatitis B, diphtheria, tetanus, acellular pertussis and inactivated poliovirus vaccine (DTaP-IPV) and measles, mumps and rubella (MMR) vaccines. There are limited studies on these vaccines in lupus patients as they are generally administered during early childhood, usually prior to the onset of SLE.

The BCG and MMR vaccines are both live vaccines are contraindicated in immunocompromised patients and not generally recommended for patients with SLE. In a pediatric study, measles antibody levels in the lupus patients (having received vaccinations before SLE onset) were similar to healthy controls. Immunizations should instead be recommended for close contacts of vulnerable patients to reduce the risk of transmission [56]. Reassuringly, transmission of attenuated vaccine strains from immunized individuals has not been reported.

The hepatitis B vaccination is a recombinant hepatitis B surface antigen with aluminum adjuvants, which may be a single-antigen or combined with other vaccines (such as hepatitis A). Despite prior reports of an increase in rheumatic disorders after hepatitis B vaccination, a causal relationship has not been established [57]. A prospective study did not find any association between hepatitis B vaccination with disease flares/activity or immunosuppressive requirements, and reported comparable protective antibodies compared with the normal adult population [58]. Given the endemicity of hepatitis B in Hong Kong as well as the intrinsic risk of viral reactivation with immunosuppression, we recommend universal vaccinations for all patients as per local guidelines and mop-up vaccinations for those previously unvaccinated individuals [59]. Vaccine responses should be assessed postvaccination after 1–2 months following completion of vaccination. A hepatitis B surface antibody (anti-HBs) level of >10 mIU/mL is generally regarded as protective and patients who do not achieve this level should be revaccinated. Persistent failure of achieving protective anti-HBs levels after repeat vaccination is unusual for SLE and such patients can be referred to an Immunologist for review. There is little data that specifically suggests lupus patients are at increased risk of waning immunity to hepatitis B, but generally postvaccination testing every 6–12 months has been advised in immunocompromised individuals [60].

The DTaP contains diphtheria and tetanus toxoids and acellular pertussis vaccine. SLE patients demonstrate effective antibody responses and immune protection against diphtheria and tetanus, which are comparable to the healthy population [61]. Lupus disease activity was unaffected by immunization following tetanus toxoid vaccination [62]. There is lack of specific evidence evaluating the efficacy or safety of pertussis vaccination in lupus patients. In contrast to the live attenuated oral polio vaccine, the injected IPV is safer but has lower immunogenicity. In a retrospective study, 5% of lupus patients developed disease flares after polio vaccination [63]. The poliovirus is nearly eradicated in most of the world, and vaccinations are only recommended unless previously unvaccinated patients plan to travel to polio-endemic areas.

CONCLUSIONS

Ensuring up-to-date and recommending appropriate vaccinations should be standard-of-care for all rheumatology patients, including SLE. The most common vaccinations, including influenza, pneumococcal, HPV and zoster, have clear evidence and recommendations for administration. In Hong Kong, the greatest barrier to appropriate vaccinations likely remains with physician awareness or willingness for recommendation. Delayed vaccinations not only increase the duration of susceptibility to infection but use of immunosuppressants in the treatment of SLE may theoretically blunt vaccination responses. Therefore, with exception for the live vaccines (such as the live attenuated zoster vaccine, which should be

considered in a case-by-case basis prior to availability of the recombinant version), these vaccinations should be offered as early as possible especially prior to initiating or augmenting immunosuppressive therapy. Prospective studies into the barriers of vaccinations and the implementation of vaccination protocols will be needed to improve the vaccination rates and protection for SLE patients in the future.

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CONFLICT OF INTEREST

Both authors disclose no conflicts of interest.

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