Primary varicella zoster virus (VZV) infection or chickenpox is typically a benign illness in immunocompetent individuals. Reactivation of latent VZV, herpes zoster (HZ), usually manifests as shingles in a restricted dermatomal distribution. However, the risk of life-threatening complications, such as disseminated VZV, is greater in immunosuppressed individuals, with significant rates of mortality. In these patients, skin lesions may be minimal, or even absent, leading to delayed diagnosis and intervention [1]. Up to 8% of patients hospitalized with VZV infection are receiving immunosuppressive therapies [2]. The case fatality rate is 10% in severely immunocompromised individuals, compared with 0.009% for all cases [3]. The British Society for Rheumatology Biologics Register revealed that the incidence of shingles is 1.6 per 100 patient-years (2% per year) in RA patients receiving anti-TNF-α therapy [4]. Data for less potent immunosuppression are more uncertain [1].

VZV vaccines are safe and efficacious at reducing varicella-related morbidity and mortality in immunocompetent individuals. In the UK, VZV vaccines for primary prevention are not administered on the childhood immunization schedule. The HZ vaccine has recently been introduced for people aged 70 for shingles prevention, with a catch-up programme at 79 years of age [5]. Vaccine effectiveness decreases substantially for those >80 years of age, and although the vaccine is licensed for those >50 years of age, due to limited vaccine supply, the above schedule is recommended for cost-effectiveness [5].

Patients with autoimmune disease are at increased risk of VZV from both the underlying disease process itself and the use of immunomodulation. While these patients may benefit most from vaccination, varicella and zoster vaccines are live attenuated therapies, which increase the risk of vaccine-related complications in patients receiving immunomodulatory agents. This raises a number of issues regarding the clinical utility of vaccinating such patients.

Depending upon the degree of underlying immunosuppression, the immunogenic response to vaccination may be diminished and efficacy may be variable [6]. The safety of live attenuated vaccines in immunosuppression is uncertain and uncontrolled replication of the vaccine strain may occur. Furthermore, the varicella virus vaccine summary of product characteristics (SPC) contains reports of vaccine virus transmission to immunocompromised household contacts, sometimes without a breakthrough rash. Reassuringly, the vaccine strains are sensitive to acyclovir. In primary care, HZ vaccine is usually administered alongside the flu vaccine. The safety and efficacy of giving multiple vaccinations in the immunocompromised state is unknown. Vaccinated patients should therefore be counselled regarding these uncertainties, advised to avoid chickenpox exposure and be monitored for signs of VZV infection should exposure occur.

Current guidance is variable and is summarized in Table 1. The UK Department of Health (DoH) generally precludes the use of live attenuated vaccines in immunosuppressed individuals with the exception of HZ vaccine [5]. The Centers for Disease Control and Prevention [7] in the USA maintains that live vaccines should be avoided only in severely immunocompromised individuals. The European League Against Rheumatism guidance [8] recommends avoidance of live attenuated vaccines in immunocompromised patients whenever possible, but VZV vaccines are considered an exception and may be considered in mildly immunosuppressed patients on a case-by-case basis.

The level of immunosuppression potentially contributing to direct harm from live attenuated vaccines is unknown. This is further complicated by the use of combination immunosuppressive therapies. Additionally, the SPC for the various immunomodulatory agents also varies. The picture is further complicated by the significant variation in guidance between different specialties such as rheumatology, gastroenterology, dermatology and paediatrics.

Definitive evidence on the clinical utility of live vaccinations is limited, however, in our practice we take the following approach to varicella vaccination. Primary varicella vaccination is not necessary for adults born and raised in the UK, as ~90% have varicella immunity from chickenpox contracted in childhood. A detailed history can elicit this information. For uncertain cases, IgG serology can be performed within 24 h, costing less than £10 in most laboratories. For non-immune patients, administering VZV vaccination would necessitate a delay of at least 2 weeks before commencing immunosuppressive therapy. This potential delay may be unacceptable in a minority of patients with severe organ-threatening autoimmune disease, with the majority of patients gaining potential long-term benefits from this proactive approach. The risks of developing infection with the VZV vaccine strain in immunosuppressed patients who are serologically naive are high. Therefore, in keeping with the DoH recommendations [5], we would not recommend VZV or HZ vaccination in those without previous chickenpox exposure who are already immunosuppressed. However, we would re-emphasize the importance of taking a careful...
history for primary VZV infection, serological testing and vaccination, if indicated, prior to initiating immunosuppression.

Secondary varicella prevention, however, requires a different approach. For immunocompromised patients with primary immunity, the risk of disseminated HZ is significant. Therefore we recommend considering HZ vaccination for all immunosuppressed patients, irrespective of age. The decision of whether to vaccinate outside of the licensing age restrictions and DoH guidance should be made on a case-by-case basis, depending upon the individual’s risk of HZ versus the risks of vaccination. Advice from an immunologist or infectious disease physician may aid in this decision-making process.

We would recommend HZ vaccination at least 2 weeks prior to immunosuppression where possible. For those already on immunosuppression, the uncertainties should be discussed with the patient in a secondary care setting and administered following the guidance in Table 1. For other anti-rheumatic drugs and biologic therapies there is no formal guidance. Observational studies [9, 10] have not demonstrate an increased risk of HZ in those who received vaccination on anti-TNF agents, however, until further evidence becomes available, we would advise caution with more potent immunosuppression.

In conclusion, we feel that guidance based on the type and intensity of immunosuppression would help clarify confusion and ensure a unified approach to patient care. Until the development of an efficacious inactivated VZV vaccine, we will continue to face the difficult decision of whether or not to vaccinate our immunocompromised patients. Presently the consensus appears to be that using live vaccines for shingles prevention is appropriate and safe in the majority of patients treated for rheumatological conditions.

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**Table 1** Summary of VZV screening and vaccination recommendations

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Evidence for immunity: recommended screening assessment</th>
<th>Vaccination recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK DoH (2013)</td>
<td>Prior (self-reported) history of chickenpox, shingles or vaccination. Serological testing for uncertain cases or individuals born outside UK.</td>
<td>Primary VZV vaccine: administer before starting immunosuppression. If already on low-dose corticosteroids (&lt;40 mg/day for &lt;1 week) or other immunosuppressive drugs, vaccinate after stopping therapy for at least 3 and 6 months, respectively, after seeking specialist physician opinion. HZ vaccination: Ideally administer before starting immunosuppression. Recommended in those on low-dose corticosteroids/ corticosteroids as replacement for adrenal insufficiency, MTX (&lt;0.4 mg/kg/week) or AZA (&lt;3.0 mg/kg/day).</td>
</tr>
<tr>
<td>CDC (2011)</td>
<td>Prior history (as per medical practitioner) of chickenpox, shingles or documentation confirming vaccination. Serological testing for uncertain cases. Serological testing after vaccination is not routinely recommended, as it may give false negative results.</td>
<td>Vaccination of at-risk household contacts is recommended, and if breakthrough rash occurs, direct contact with at-risk individuals should be avoided. HZ vaccination: vaccination recommended for those on low-dose MTX (&lt;0.4 mg/kg/week) or AZA (&lt;3.0 mg/kg/day). Avoid live vaccination whenever possible, although varicella and zoster vaccines can be considered exceptions to this rule for those who are mildly immunosuppressed on anti-rheumatic drugs on a case-by-case basis. Temporary discontinuation of immunosuppression may be considered, but there is no supporting evidence.</td>
</tr>
<tr>
<td>EULAR (2010)</td>
<td>Serological testing for primary VZV prior to zoster vaccine.</td>
<td>Vaccination whenever possible, although varicella and zoster vaccines can be considered exceptions to this rule for those who are mildly immunosuppressed on anti-rheumatic drugs on a case-by-case basis. Temporary discontinuation of immunosuppression may be considered, but there is no supporting evidence.</td>
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</tbody>
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DoH: Department of Health; VZV: varicella zoster virus; HZ: herpes zoster; CDC: Centers for Disease Control and Prevention; EULAR: European League Against Rheumatism.
References


