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Review

# Safety of live vaccinations on immunosuppressive therapy in patients with immune-mediated inflammatory diseases, solid organ transplantation or after bone-marrow transplantation – A systematic review of randomized trials, observational studies and case reports

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ABSTRACT

*Background:* Live vaccines are generally contraindicated on immunosuppressive therapy due to safety concerns. However, data are limited to corroborate this practice.
*Objectives:* To estimate the safety of live vaccinations in patients with immune-mediated inflammatory diseases (IMID) or solid organ transplantation (SOT) on immunosuppressive treatment and in patients after bone-marrow transplantation (BMT).
*Data Sources:* A search was conducted in electronic databases (Cochrane, Pubmed, Embase) and additional literature was identified by targeted searches.
*Eligibility criteria:* Randomized trials, observational studies and case reports.
*Population:* Patients with IMID or SOT on immunosuppressive treatment and BMT patients <2 years after transplantation.
*Intervention/vaccinations looked at:* Live vaccinations: mumps, measles, rubella (MMR), yellow fever (YF), varicella vaccine (VV), herpes zoster (HZ), oral typhoid, oral polio, rotavirus, Bacillus Calmette–Guérin (BCG), smallpox.
*Data extraction:* One author performed the data extraction using predefined data fields. It was cross-checked by two other authors.
*Results:* 7305 articles were identified and 64 articles were included: 40 on IMID, 16 on SOT and 8 on BMT patients. In most studies, the administration of live vaccines was safe. However, some serious vaccine-related adverse events occurred. 32 participants developed an infection with the vaccine strain; in most cases the infection was mild. However, in two patients fatal infections were reported: a patient with RA/SLE overlap who started MTX/dexamethasone treatment four days after the YFV developed a yellow fever vaccine-associated viscerotropic disease (YEL-AVD) and died. The particular vaccine lot was found to be associated with a more than 20 times risk of YEL-AVD. One infant whose mother was under infliximab treatment during pregnancy received the BCG vaccine at the age of three months and developed disseminated BCG infection and died. An immunogenicity assessment was performed in 43 studies. In most cases the patients developed satisfactory seroprotection rates. In the IMID group, YFV and VV demonstrated high seroconversion rates. MTX and tumor necrosis factor inhibitory therapy appeared to reduce immune responses to VV and HZ vaccine, but not to MMR and YF-revaccination. Seroconversion in SOT and BMT patients showed mostly higher rates for rubella than for measles, mumps and varicella.

*Abbreviations:* AEs, adverse events; BCG, Bacillus Calmette–Guérin; BMT, bone marrow transplantation; CSA, cyclosporine A; GvHD, graft versus host disease; HZ, herpes zoster; HZV, herpes zoster vaccine; IBD, inflammatory bowel disease; IFX, infliximab; IMID, immune-mediated inflammatory disease; INF, interferon; IVIG, intravenous immunoglobulin; JIA, juvenile idiopathic arthritis; MMF, mycophenolate-mofetil; MMR, mumps, measles, rubella; MS, multiple sclerosis; MTX, methotrexate; RA, rheumatoid arthritis; RCT, randomized controlled trial; RTX, rituximab; SAE, serious adverse event; SLE, systemic lupus erythematosus; SOT, solid organ transplantation; TAC, tacrolimus; TCZ, tocilizumab; TNFi, tumor necrosis factor inhibitor; VV, varicella vaccine; VZV, varicella zoster virus; YEL-AVD, yellow fever vaccine-associated viscerotropic disease; YF, yellow fever; YFV, yellow fever vaccine.

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*Limitations:* Risk of bias was high in the majority of studies since 39 of them were observational and 17 were case series/case reports. Only eight studies were randomized trials. BMT patient numbers included in this review were low.
*Conclusions:* Although live vaccinations were safe and sufficiently immunogenic in most studies, some serious reactions and vaccine-related infections were reported in immunosuppressed IMID and SOT patients. Apart from mild vaccine-related infections MMR and VV vaccines were safe when administered less than two years after BMT.
*Implications of key findings:* Until further data are available, live vaccinations under most immunosuppressive treatments should only be administered after a careful risk benefit assessment of medications and dosages.
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**Contents**



## 1. Introduction

Immunizations are an important means for preventing infectious diseases in healthy individuals and especially in vulnerable patient groups with immunocompromising conditions. However, live vaccinations contain an attenuated vaccine strain, which has the theoretical potential to revert to the original pathogenic form and to induce infection by the vaccine strain, particularly in immunocompromised individuals. Serious infections with the vaccine strain and even deaths have occurred in HIV patients, leukemia patients and patients with inherited immunodeficiencies [1–4].

The number of individuals treated with immunosuppressive medications due to immune-mediated inflammatory diseases (IMID), solid organ transplantation (SOT) or patients after bone-marrow transplantation (BMT) has grown over the last decades [5]. Clinicians are increasingly exposed to the dilemma on whether an immunosuppressed patient can receive a live vaccine – which is very important as severe infections with infections preventable by live vaccinations such as measles and varicella can occur on immunosuppressive therapy [6,7]. On the other hand, the live vaccine itself may impose a danger to the immunosuppressed individual. Furthermore, vaccines may be less effective when administered to an impaired immune system [8].

To date, live vaccines are contraindicated under most immunosuppressive therapies. However, data are generally scarce. Over the last few years efforts have been made to evaluate the safety of some live vaccines in selected immunosuppressed individuals by conducting both, retrospective and prospective studies. Further data have become available as live vaccines were occasionally administered inadvertently or after a careful risk–benefit assessment to individual patients.

In this systematic review, we aim to provide an overview on the results of published randomized trials, observational studies and case reports on live vaccinations in patients with IMIDs or SOT on immunosuppressive therapy as well as BMT patients who