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**None declared.**

# Do We Receive Cytomegalovirus Vaccination Before Solid Organ Transplant: a Meta-Analysis

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**Review question / Objective:** **We compared cytomegalovirus (CMV) vaccination for solid organ transplantation recipients ( SOTs) with placebo treatment, to investigate the efficacy and safety for the prevention of CMV infection in SOTs.**
**Condition being studied:** **Patients after solid organ transplantation subsequently become immunosuppressed, and cytomegalovirus (CMV) is the most common opportunistic pathogen to this population. The prevalence of CMV infection can reach 50% in the general population, and further up to 64-72% in solid organ transplant recipients (SOTs). CMV seropositive donors (CMV D+) puts even more pressure of CMV infection for SOTs. Post-transplant CMV infection can lead to neutropenia, lymphopenia, thrombocytopenia, tissue/end-organ invasive CMV disease (gastroenteritis, pneumonia, hepatitis, encephalitis), other infectious diseases, graft dysfunction, and multiple organ failure. CMV can disturb immune cell function, thus is one of the major risk factors that increase mortality within 6 months after transplantation. However, practical, effective method to prevent postoperative CMV infection for SOTs remains unresolved. Vaccination of CMV is only at clinical trials stage. To date, there is a lack of guidelines or consensus for preventing CMV disease for SOTs. Given the increasing clinical trials of CMV vaccination, it is important to clarify the evidence-based benefits and risks of CMV vaccination for SOTs, and to provide the best CMV disease prevention measurements.**

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 November 2022 and was last updated on 28 November 2022 (registration number INPLASY2022110143).

## INTRODUCTION

**Review question / Objective:** **We compared cytomegalovirus (CMV) vaccination for solid organ transplantation recipients ( SOTs) with placebo treatment, to investigate the efficacy and safety for the prevention of CMV infection in SOTs.**

**Rationale:** **Cytomegalovirus (CMV) is one of the most devastating opportunistic infections for solid organ recipients (SOTs).**

To date, there is no guideline or consensus to propose any effective prevention and treatment method for CMV disease for SOTs. Some clinical trials of CMV vaccines for SOTs are promising.

**Condition being studied:** Patients after solid organ transplantation subsequently become immunosuppressed, and cytomegalovirus (CMV) is the most common opportunistic pathogen to this population. The prevalence of CMV infection can reach 50% in the general population, and further up to 64-72% in solid organ transplant recipients (SOTs). CMV seropositive donors (CMV D+) puts even more pressure of CMV infection for SOTs. Post-transplant CMV infection can lead to neutropenia, lymphopenia, thrombocytopenia, tissue/end-organ invasive CMV disease (gastroenteritis, pneumonia, hepatitis, encephalitis), other infectious diseases, graft dysfunction, and multiple organ failure. CMV can disturb immune cell function, thus is one of the major risk factors that increase mortality within 6 months after transplantation. However, practical, effective method to prevent postoperative CMV infection for SOTs remains unresolved. Vaccination of CMV is only at clinical trials stage. To date, there is a lack of guidelines or consensus for preventing CMV disease for SOTs. Given the increasing clinical trials of CMV vaccination, it is important to clarify the evidence-based benefits and risks of CMV vaccination for SOTs, and to provide the best CMV disease prevention measurements.

## METHODS

**Search strategy:** Our study followed the updated PRISMA 2020 guidelines for meta-analysis[8]. Two reviewers searched published trials comparing CMV vaccination to placebo, control, or antiviral treatment for SOTs in PubMed, Wiley Online Library, Medline, and Web of Science database up to November 2022. Keywords included "cytomegalovirus vaccination", or "CMV vaccine", or “gB/MF59”, or “TransVax”, or “LACV”, combined with "solid organ transplants", or “solid organ transplant recipient”, or “solid organ candidate”, or “heart transplantation”, or “kidney transplantation”, or “lung transplantation”, or “liver transplantation”, and with "immunogenicity", or "immunization" were used in the searches. Relevant literature in the reference lists and conference proceedings were also included. There was no restriction on language or publication date.

**Participant or population:** SOTs who received CMV vaccination or placebo before or after transplantation.

**Intervention:** Patients were divided into CMV vaccination group and placebo group.

**Comparator:** Main outcome measurements: Primary outcome was defined as CMV infection. Secondary outcomes included: CMV viremia, CMV disease, severe CMV disease, allograft rejection, and 5-year-survival. CMV viremia was detected by viral isolation or quantified CMV viral load testing. CMV disease (also described as CMV syndrome or CMV tissue-invasive disease) was diagnosed when CMV infected patients exhibited symptoms such as fever, myelosuppression, pneumonia, hepatitis, hepatitis, renal insufficiency, encephalitis, superinfection, etc. Severe CMV disease was defined as CMV disease scoring≥7.

**Study designs to be included:** We searched studies involving CMV vaccination in SOTs, with or without application of antiviral treatment.

**Eligibility criteria:** Inclusion criteria: 1. controlled trials or cohort study; 2. peer-reviewed journals; 3. CMV vaccination compared with placebo, or routine medical care, or compared with antiviral treatment (prophylaxis or pre-emptive treatment) for SOTs (regardless of age). Exclusion criteria: 1. animal studies; 2. observational studies, case-report, or other studies that do not include comparedgroup.

**Information sources:** Two reviewers independently searched the database

according to the keywords. Studies suitable for inclusion referred as controlled trials or cohort study involving CMV vaccination for SOTs. After screening titles and abstracts, studies were primarily retrieved in accordance with inclusion criteria based on Jadad scale. Further manual search was also performed. Judged by the reviewers, relevant articles from the reference list and similar articles during literature retrieval were also included. When important data were missing, we contacted the authors to clarify the reason and re-evaluated the article for inclusion. If study data were duplicated, articles covering the largest sample or with the most comprehensive data were selected for inclusion. Discrepancies were discussed and consulted through a third reviewer.

**Main outcome(s):** Primary outcome was defined as CMV infection.

**Additional outcome(s):** Secondary outcomes included: CMV viremia, CMV disease, severe CMV disease, allograft rejection, and 5-year-survival. CMV viremia was detected by viral isolation or quantified CMV viral load testing. CMV disease (also described as CMV syndrome or CMV tissue-invasive disease) was diagnosed when CMV infected patients exhibited symptoms such as fever, myelo-suppression, pneumonia, hepatitis, hepatitis, renal insufficiency, encephalitis, superinfection, etc. Severe CMV disease was defined as CMV disease scoring≥7.

**Data management:** Pooled data were analyzed using Review Manager (Version 5.4. The Cochrane Collaboration, 2020). Outcome variables in our meta-analysis were dichotomous. Relative risks were calculated using random effects models, estimated by Mantel–Haenszel method. Pooled dichotomous data were expressed as relative risk (RR) with 95% confidence interval (CI). Cochran's Q test and I2 statistics were applied to detect variations due to heterogeneity among studies. Subgroup analyses were performed to explore the difference of CMV infection between groups in the population of high-risk SOTs (donor seropositive, recipient seronegative, or recipient seropositive, D+/R- or R+) and low-risk SOTs (donor seronegative, recipients seronegative, D-/R-), respectively. Post hoc sensitivity analyses were performed by exclusion of data from certain studies. The effectiveness of different types of CMV vaccine was compared by chi-squared test. $P<0.05$ was considered statistically significant.

**Quality assessment / Risk of bias analysis:** All three reviewers independently graded the trial quality, which included the scoring of sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective reporting (reporting bias). Bias estimation was determined by the judgment of the majority. Publication bias was evaluated by funnel plot analysis.

**Strategy of data synthesis:** We counted the prevalence of CMV infection, CMV disease, and severe CMV disease. Efficacy assessment also included survival. Safety assessment included adverse events and allograft rejection. Pooled dichotomous data were expressed as relative risk (RR) with 95% confidence interval (CI). Cochran's Q test and I2 statistics were applied to detect variations due to heterogeneity among studies.

**Subgroup analysis:** Subgroup analyses were performed to explore the difference of CMV infection between groups in the population of high-risk SOTs (donor seropositive, recipient seronegative, or recipient seropositive, D+/R- or R+) and low-risk SOTs (donor seronegative, recipients seronegative, D-/R-), respectively.

**Sensitivity analysis:** Post hoc sensitivity analyses were performed by exclusion of data from certain studies.

**Language restriction:** There was no language restriction.

**Country(ies) involved:** China.

**Keywords:** cytomegalovirus; CMV disease; vaccination; solid organ transplant; randomized control trial; meta-analysis.

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