



## Review

# Vaccinating donors for hematopoietic cell transplantation: A systematic review and future perspectives



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## ABSTRACT

Allogeneic hematopoietic cell transplantation (Allo-HCT) recipients are at an increased risk of infectious complications, which is a major cause of morbidity and mortality post-transplant. Vaccination of donors is one of the strategies that has been studied to improve immune reconstitution post-transplant, however the efficacy and safety of this strategy is not well reviewed in the literature. In this systematic review we sought to evaluate the current strategies of donor vaccination along with their immunogenicity, effectiveness and safety. Utilizing strict selection criteria with defined MeSH terminology, an electronic search was conducted from the following databases: Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and Scopus. Abstracts of various professional society meetings were also screened and hand searching of various reviews and guideline articles was carried out. The full text of 52 articles were reviewed, from which 5 articles satisfied the inclusion/exclusion criteria for effectiveness and immunogenicity trials and 1 article was included for safety data. Jadad score was used to assess the quality of included studies. The results of the included studies were inconsistent, and the studies were generally of suboptimal methodological quality. Most of the included studies (n = 3) investigated the use of more than one vaccine, however not all commonly used vaccines in HCT were investigated. None of the studies reported any long-term benefits for HCT recipients of vaccinated donors. Only one study reported safety data of using vaccination in donors. Given the suboptimal quality of the studies, and questionable effectiveness, donor vaccination cannot be recommended for all. Prospective high-quality vaccine trials in HCT donors are needed.

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## 1. Introduction

Allogeneic hematopoietic cell transplant (Allo-HCT) recipients are at risk of many early and late complications. Immunologic and infectious complications are still major challenges, despite of all the advances in HCT [1,2]. The recovery of Allo-HCT recipient's innate immunity usually takes months, whereas the recovery of adaptive immunity takes 1–2 years [3,4]. Moreover, those durations might be delayed in certain patients including Graft-versus-host disease (GVHD) patients, and such delays constitute a major cause of post-transplant morbidity and mortality. This puts HCT recipients at risk of infections including those which are vaccine preventable [1,4–7]. Thus, different strategies have been investigated to improve immune reconstitution in Allo-HCT recipients including recipient revaccination and donor vaccination [3].

Titers of protective antibodies that were elicited by pre-transplant vaccination are generally low or absent post HCT [8,9]. Reviews and guidelines mainly addressing post-transplant vaccination have been published by different institutions/organizations including: Infectious Diseases Society of America (IDSA), American Society for Blood and Marrow Transplantation (ASBMT) and European Group of Blood and Marrow Transplantation (EBMT), as well as others. Despite the limited evidence on the efficacy of post-transplant vaccination, revaccination is recommended by majority of the guidelines, starting from 3 to 6 months for inactivated and toxoid vaccines, and 24 months for live-attenuated vaccines [9–13]. Recommendations for donor vaccination, on the contrary are scarce, and in absence of documented safety and compelling evidence for recipient benefit, their use faces logistical and ethical challenges [3,14].

Many studies have demonstrated donor origin of post-transplant humoral and cellular immunity for different infections, showing the adoptive transfer of donor immunity to HCT recipients [15–19]. Many more recent articles have investigated the effect of donor vaccination on recipient's post-transplant immunity. This systematic review aims to provide a better understanding of the current evidence on the efficacy and safety of donor vaccination in improving recipient's immunological and clinical performance post-transplant.

## 2. Materials and methods

### 2.1. Data sources and search strategies

The electronic search strategy was comprehensive targeting all the studies performed on HCT vaccination strategies from 1980 to

October 2017. The search included only English language, and the databases searched included: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to October 2017, EBM Reviews – Cochrane Central Register of Controlled Trials October 2017, EBM Reviews – Cochrane Database of Systematic Reviews 2005 to October 2017 and SCOPUS. The search strategies used Boolean logic with terminology including: “Bone Marrow Transplantation” and “Hematopoietic Stem Cell Transplantation” in combination with both general terms like: “Vaccination”, “Immunization”, etc. and terms for specific vaccines like: “Measles-Mumps-Rubella Vaccine”, “Rotavirus Vaccines”, etc. Additionally, top results of more robust search engines were screened, including: Google Scholar and a medical library federated search that involves 8 additional databases (for peer-reviewed journal articles only). The abstracts of the professional society meetings of American Society of Hematology, American Society for Blood and Marrow Transplantation, European Hematology Association, and European Society for Blood and Marrow Transplantation were reviewed to avoid any publication bias. Lastly, hand searching of relevant review studies and guideline papers was done to avoid missing any article by the search strategies. (Refer to [Supplemental materials](#) for more details).

### 2.2. Inclusion criteria

Publications to be included in this review had to be studies with a primary objective of investigating the effect of HCT donors' vaccination effectiveness and immunogenicity or safety. Included studies for effectiveness and immunogenicity data, satisfied the following: (1) They were primary research, not secondary data/review from other studies. Review articles and meta-analyses were excluded from the review. However, relevant reviews' references were screened. (2) They had an experimental design (donor vaccinated under the study protocol) with at least two different research groups, one of which had a vaccinated donor and a control group in which the donor was unvaccinated. Observational studies and studies that had only donor immunity status as an analytical variable were not included, however they were discussed in the review text to give additional insights on the topic. (3) Quantitative analysis comparing the two groups was done and the outcome was presented numerically or in a form of numerical representations (i.e. figures and graphs). (4) Studies on human subjects only. Animal studies and laboratory in vitro studies were excluded. (5) Publication year specified to be from 1980 until October 2017; English language articles only. (6) Studies were included regardless

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