Serologic Vaccination Response after Solid Organ Transplantation: A Systematic Review

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Abstract

Background: Infectious diseases after solid organ transplantation (SOT) are one of the major complications in transplantation medicine. Vaccination-based prevention is desirable, but data on the response to active vaccination after SOT are conflicting.

Methods: In this systematic review, we identify the serologic response rate of SOT recipients to post-transplantation vaccination against tetanus, diphtheria, polio, hepatitis A and B, influenza, Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitides, tick-borne encephalitis, rabies, varicella, mumps, measles, and rubella.

Results: Of the 2478 papers initially identified, 72 were included in the final review. The most important findings are that (1) most clinical trials conducted and published over more than 30 years have all been small and highly heterogeneous regarding trial design, patient cohorts selected, patient inclusion criteria, dosing and vaccination schemes, follow up periods and outcomes assessed, (2) the individual vaccines investigated have been studied predominately only in one group of SOT recipients, i.e. tetanus, diphtheria and polio in RTX recipients, hepatitis A exclusively in adult LTX recipients and mumps, measles and rubella in paediatric LTX recipients, (3) SOT recipients mount an immune response which is for most vaccines lower than in healthy controls. The degree to which this response is impaired varies with the type of vaccine, age and organ transplanted and (4) for some vaccines antibodies decline rapidly.

Conclusion: Vaccine-based prevention of infectious diseases is far from satisfactory in SOT recipients. Despite the large number of vaccination studies preformed over the past decades, knowledge on vaccination response is still limited. Even though the protection, which can be achieved in SOT recipients through vaccination, appears encouraging on the basis of available data, current vaccination guidelines and recommendations for post-SOT recipients remain poorly supported by evidence. There is an urgent need to conduct appropriately powered vaccination trials in well-defined SOT recipient cohorts.

Introduction

The numbers of solid organ transplant (SOT) recipients have substantially increased in recent decades. Transplant rejection rates decreased with improved immunosuppression and quality of life increased with better post-transplant care. Donor- and recipient- derived, opportunistic, nosocomial or community acquired infections including newly emerging infectious diseases and malignancies remain a problem, however [1,2]. Most infections in SOT recipients are associated with high morbidity and mortality compared to immunocompetent individuals. Furthermore, more powerful immunosuppressive drugs, such as biologic agents are changing the pattern of infection with new, previously unknown infection risks [3,4].

Vaccination is the most efficient and cost effective intervention to prevent infectious diseases in healthy persons [5]. The response to vaccines with subsequent protection against infectious diseases, however, is depending on a functioning immune system.

Despite current recommendations emphasizing the importance of vaccinating SOT candidates prior to transplantation, reality tells a different story: vaccine coverage studies have demonstrated that this goal is far from being achieved. In the pre-transplantation phase practical problems of timely vaccination are difficult to overcome and concerns by both patients and doctors about vaccine-induced side effects are the main reason for the reluctant vaccination uptake in the post-transplantation period [6,7].

Guidelines and recommendations for vaccination of SOT recipients are poorly supported by evidence and are largely extrapolated from what is known for healthy persons. For new immunosuppressive regimens and recently approved vaccines, recommendations are solely based on theoretical considerations.
We systematically review published data on the vaccination response of SOT recipients to summarize current knowledge and to identify areas where research is needed.

**Methods**

**Search Strategy**
We systematically reviewed published work in accordance with the PRISMA guidelines [8]. We performed an electronic search with the following medical subject heading (MESH) terms: “immunization”, “vaccination” and “organ transplantation” in PubMed, Embase and Cochrane Central Register of Controlled Trials without time restriction till end of December 2011. The search was restricted to articles on human research and English language. References of the papers identified and of relevant reviews and books were additionally searched.

**Trial Selection**
We included original research papers published in peer-reviewed scientific journals reporting results on adult or paediatric SOT recipients that were vaccinated with currently licensed vaccines (see Table 1). We included all studies in which vaccination appeared warranted as defined by those who designed and conducted the study. This definition included studies where SOT recipients were considered unvaccinated in the pre-transplant era, SOT recipients whose vaccination status was not updated before transplantation, SOT recipients with negative antibody status or with unknown vaccination status.

Serologic immune response to vaccination had to be assessed at least once after vaccination. All types of vaccines that are currently in use independent of the vaccination schedule, combination and dosing were accepted. No restriction regarding study design was applied.

We excluded studies on vaccination of transplant candidates or organ donors, experimental vaccines or adjuvants, comparative trials on routes of application, trials on vaccines that are out of use and trials on pandemic vaccines. We excluded articles where humoral (serologic) response was not assessed, key data were missing or not extractable (number of SOT recipients vaccinated, rate of response, and time of vaccination), when no primary data were given (all reviews, editorials, guidelines, letter to the editor and comments), case and conference reports. Further, we excluded trials on vaccination for prevention of hepatitis B recurrence due to HBV-related liver disease, transplant recipients with a history of HBV infection or anti-HBc positive grafts. If the same group of

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**Table 1. Criteria and definitions for study selection and data analysis.**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Inclusion criteria</td>
<td>Active vaccination</td>
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<td></td>
<td>Licensed vaccine still in use</td>
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<td></td>
<td>Adult or paediatric SOT recipients on immunosuppressive medication</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>Vaccination of solid organ transplant candidates or donors</td>
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<td></td>
<td>Experimental vaccines</td>
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<td>Experimental adjuvants</td>
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<td></td>
<td>Comparative trials on routes of vaccine application</td>
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<td></td>
<td>Vaccines out of use</td>
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<td></td>
<td>Pandemic vaccines</td>
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<tr>
<td></td>
<td>Humoral (serologic) response not assessed</td>
</tr>
<tr>
<td></td>
<td>Key data missing (number of vaccines, rate of response, and time of vaccination)</td>
</tr>
<tr>
<td></td>
<td>No primary data given (reviews, editorials, guidelines, letter to the editor and comments on other articles)</td>
</tr>
<tr>
<td></td>
<td>Case reports</td>
</tr>
<tr>
<td></td>
<td>Conference reports</td>
</tr>
<tr>
<td></td>
<td>Trials on prevention of HBV recurrence in liver graft recipients with a history of HBV infection or anti-HBc positive grafts.</td>
</tr>
</tbody>
</table>

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*If a shorter time interval was accepted exceptionally, this is indicated in the text or by a footnote.*

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SOT recipients was described in more than one article, only the report with the more detailed data presentation was included.

All articles obtained in the search were reviewed on the basis of the title in a first step, if the title was unclear, the abstract was additionally reviewed (exclusion step one). After subtraction of duplicates, articles were checked for inclusion criteria on the basis of the abstract or the full text (exclusion step two). Articles not fulfilling the inclusion criteria were excluded (exclusion step three). Hard copies of the articles fulfilling all inclusion criteria were obtained and the data extracted with a data extraction sheet. Additionally, the reference list of relevant articles and reviews were searched (for data flow, see Figure 1). Both authors performed all selection steps independently.

Data Extraction

From all articles remaining after exclusion step two the following data were extracted: Type of trial, type of SOT, age-group of SOT recipients (adult/paediatric), type of vaccine, vaccination schedule (number of doses and timing), number of SOT recipients and controls vaccinated, proportion of subjects (SOT recipients and, if given, controls) with vaccine response, time of follow up (defined time interval between vaccination and serological tests), cut-offs used for definition of vaccine response and immunosuppressive regimen.

Data Analysis

As outcome of interest we choose the serologic response to vaccination and report the overall proportion of SOT recipients with vaccine response at two time points after vaccination. For our analysis the vaccination response defined by the authors of the individual studies was accepted as valid. Short-term response was defined as the humoral (serological) vaccine response measured as rate of seroconversion where this information is available, or as serological response defined as “protective” by the authors two weeks to three months after vaccination. Long-term response was defined as humoral (serological) vaccine response measured after 12 months or longer. If a shorter time interval was exceptionally accepted as long-term response, this is indicated (Table 1).

For detailed analysis, we grouped all articles obtained in the following categories: category A includes all studies on vaccination against tetanus, diphtheria, and polio. Category B includes vaccination against viral hepatitis A and B (HAV and HBV). Category C includes vaccination against seasonal influenza; category D includes vaccination against bacterial pathogens (Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitides). Category E includes all live virus vaccines (mumps, measles, rubella and varicella) and category F includes vaccination against pathogens indicated in certain geographical areas (tick-borne encephalitis virus and rabies virus) (Table 2).

Forest Plot

We calculated the percentage of seropositive individuals at follow-up by dividing the number of patients with positive response by the total number of patients with exact binomial 95% confidence intervals (CIs) separately for each vaccination group in each study and displayed these in forest plots. Studies which only reported calculated percentage numbers were not included. For influenza forest plots, only studies which assessed response to every one of the three single antigens (H1N1, H3N2 and B) were included in the forest plot. We used meta-regression to compare response proportions, for example between adult and paediatric transplant recipients. The standard error for the response proportion in a study was derived from the lower and upper confidence limit of the response proportion. Serological responses in transplant patients were compared with those of comparison groups when available in each study with the use of the risk difference (RDs) and 95% CIs either assuming a common-effect by using the Mantel-Haenszel method or by using the DerSimonian and Laird random-effects meta-analysis as implemented in the “metan” command in Stata [9]. We quantified between-trial heterogeneity with use of the I-squared statistic [10].

Results

In total, we obtained 2478 articles in the search (Figure 1). Based on title, 303 potentially suitable articles of those were selected. Remained articles which were checked for duplicates, then for inclusion/exclusion criteria on the basis of abstract, or, if not all the necessary information was provided in the abstract, on the basis of the full text. From these articles, in total 233 articles were excluded.

64 articles obtained through the initial search fulfilled all inclusion criteria. By searching the reference lists of relevant articles, reviews and books, 8 papers were additionally identified. In total 72 papers were included into the review.

Of the trials that fulfilled the inclusion criteria (Table 3), publication date ranged from 1980 to 2011. There were prospective controlled (n = 32), prospective uncontrolled (n = 30), retrospective (n = 4), and randomized (n = 5) trials and, although initially defined as exclusion criteria but due to its relevance, one case report (n = 1) included in the review. Some trials used more than one trial design within the same publication on different

### Table 2. Categories of vaccinations used and rationale for grouping.

<table>
<thead>
<tr>
<th>Category</th>
<th>Vaccinations against</th>
<th>Rationale for grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Tetanus, Diphtheria, Polio</td>
<td>Inactivated vaccines which are frequently given as combined vaccination, part of regular childhood immunization scheme</td>
</tr>
<tr>
<td>B</td>
<td>Hepatitis A, Hepatitis B</td>
<td>Inactivated vaccines against viral hepatitis, available as combination vaccine</td>
</tr>
<tr>
<td>C</td>
<td>Influenza</td>
<td>The only vaccine which is indicated yearly and has a seasonally changing antigen composition, inactivated trivalent vaccine includes three different antigens (H1N1, H3N2 and B)</td>
</tr>
<tr>
<td>D</td>
<td>Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitides</td>
<td>Inactivated vaccines against bacterial pathogens, Streptococcus pneumoniae available either as polysaccharide or conjugate vaccine, response includes a large number of antigens (7 or 23 serotypes) which differ in their immunogenicity</td>
</tr>
<tr>
<td>E</td>
<td>Varicella, Mumps, Measles, Rubella</td>
<td>Attenuated live virus vaccines which are given in childhood, available as combination vaccine</td>
</tr>
<tr>
<td>F</td>
<td>Tick-borne encephalitis, Rabies</td>
<td>Vaccines which are indicated for certain geographical areas, not part of the basic vaccination scheme</td>
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doi:10.1371/journal.pone.0056974.t002
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<thead>
<tr>
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<tr>
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<td>Girndt</td>
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</tr>
<tr>
<td>Enke a)</td>
<td>1997</td>
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<tr>
<td>Huzly a)</td>
<td>1997</td>
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<tr>
<td>Ghio</td>
<td>1997</td>
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<tr>
<td>Pedrazzi a)</td>
<td>1999</td>
</tr>
<tr>
<td>Puissant-Lubrano a)</td>
<td>2010</td>
</tr>
<tr>
<td>Puissant-Lubrano b)</td>
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<tr>
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<tr>
<td>Huzly b)</td>
<td>1997</td>
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<tr>
<td>Pedrazzi b)</td>
<td>1999</td>
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<tr>
<td>Ghio</td>
<td>1997</td>
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<th>Category A: Polio</th>
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<td>Dumot</td>
<td>1999</td>
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<tr>
<td>Günther a)</td>
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<td>Günther b)</td>
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<td>Arslan</td>
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<td>Wagner</td>
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<tr>
<td>Lefebure</td>
<td>1993</td>
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<tr>
<td>Berner</td>
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<td>Chalasani</td>
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<td>Duca</td>
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<td></td>
<td></td>
<td>SOT (%)</td>
<td>HC (%)</td>
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<tr>
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<td>Lin</td>
<td>2006</td>
<td>pu</td>
<td>LTX, P</td>
<td>24/30 (80%)</td>
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<tr>
<td></td>
<td>Ni a)</td>
<td>2008</td>
<td>pu</td>
<td>LTX, P</td>
<td>7/11 (63.6%)</td>
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</tr>
<tr>
<td></td>
<td>Ni b)</td>
<td>2008</td>
<td>pu</td>
<td>LTX, P</td>
<td>4/4 (100%)</td>
<td>–</td>
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<td>SOT (%)</td>
<td>HC (%)</td>
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<tr>
<td>Briggs</td>
<td>1980</td>
<td>PC</td>
<td>RTX, A</td>
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<td>A/H3N2: 1/1 (100%)</td>
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<td>B: 1/1 (100%)</td>
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<tr>
<td>Huang</td>
<td>1983</td>
<td>PC</td>
<td>RTX, A</td>
<td>A/H1N1: 1/1 (100%)</td>
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<td>A/H3N2: 0/0 (0%)</td>
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<td>B: 1/1 (100%)</td>
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<tr>
<td>Kobashigawa</td>
<td>1993</td>
<td>PC</td>
<td>HTX, A</td>
<td>A/H1N1: 1/1 (100%)</td>
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<td>A/H3N2: 0/0 (0%)</td>
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<td>B: 0/0 (0%)</td>
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<tr>
<td>Kobashigawa</td>
<td>1993</td>
<td>PC</td>
<td>RTX, HTX, LTX, P</td>
<td>A/H1N1: 1/1 (100%)</td>
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<td>B: 0/0 (0%)</td>
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<tr>
<td>Mauch</td>
<td>1995</td>
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<td>B: 0/0 (0%)</td>
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<tr>
<td>Mack</td>
<td>1996</td>
<td>PC</td>
<td>RTX, P</td>
<td>A/H1N1: 1/1 (100%)</td>
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<td>A/H3N2: 1/1 (100%)</td>
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<td></td>
<td>B: 0/0 (0%)</td>
<td>–</td>
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<tr>
<td>Blumberg a)</td>
<td>1996</td>
<td>PC</td>
<td>RTX, LTX, HTX, A</td>
<td>A/H1N1: 1/1 (100%)</td>
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<td>A/H3N2: 0/0 (0%)</td>
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<td>B: 0/0 (0%)</td>
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<tr>
<td>Blumberg b)</td>
<td>1996</td>
<td>PC</td>
<td>RTX, LTX, P</td>
<td>A/H1N1: 1/1 (100%)</td>
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<td>A/H3N2: 1/1 (100%)</td>
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<td></td>
<td>B: 0/0 (0%)</td>
<td>–</td>
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<tr>
<td>Admon a)</td>
<td>1997</td>
<td>PC</td>
<td>RTX, P</td>
<td>A/H1N1: 1/1 (100%)</td>
<td>–</td>
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<td></td>
<td></td>
<td>A/H3N2: 1/1 (100%)</td>
<td>–</td>
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<td></td>
<td></td>
<td></td>
<td>B: 0/0 (0%)</td>
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</tbody>
</table>

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### Table 3. Cont.

**Category C: Influenza**

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Design</th>
<th>Patients</th>
<th>Short-term response SOT (%)</th>
<th>Short-term response HC (%)</th>
<th>Vaccine (Season), Vaccination scheme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admon b)</td>
<td>1997</td>
<td>pc HTX, A</td>
<td>A/H1N1: 7/17 (41%)</td>
<td>–</td>
<td>TIV (1989/90 and 1990/91) single (controls), double (SOT, month 0, 1) or triple dose (SOT, month 0, 1, 12)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>A/H3N2: 4/17 (24%)</td>
<td>–</td>
<td>TIV (1989/90 and 1990/91) single (controls), double (SOT, month 0, 1) or triple dose (SOT, month 0, 1, 12)</td>
<td></td>
</tr>
<tr>
<td>Admon c)</td>
<td>1997</td>
<td>pc HTX, A</td>
<td>A/H1N1: 12/17 (71%)</td>
<td>–</td>
<td>TIV (1989/90 and 1990/91) single (controls), double (SOT, month 0, 1) or triple dose (SOT, month 0, 1, 12)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>A/H3N2: 11/17 (65%)</td>
<td>–</td>
<td>TIV (1989/90 and 1990/91) single (controls), double (SOT, month 0, 1) or triple dose (SOT, month 0, 1, 12)</td>
<td></td>
</tr>
<tr>
<td>Dengler a)</td>
<td>1998</td>
<td>pc HTX, A</td>
<td>A/H1N1: 8/16 (50%)</td>
<td>34/35 (94.3%)</td>
<td>TIV (1991/92), single (controls) or double dose (SOT)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>A/H3N2: 10/16 (62.5%)</td>
<td>33/35 (97.1%)</td>
<td>TIV (1991/92), single (controls) or double dose (SOT)</td>
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<tr>
<td>Blumberg a)</td>
<td>1998</td>
<td>pu HTX, A</td>
<td>A/H1N1: 4/9 (44.4%)</td>
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<td>TIV (1993/1994) single dose</td>
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<tr>
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<td>A/H3N2: 5/9 (55.5%)</td>
<td>–</td>
<td>TIV (1993/1994) single dose</td>
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<td>Blumberg b)</td>
<td>1998</td>
<td>ia HTX, A</td>
<td>A/H1N1: 4/5 (80%)</td>
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<td>TIV (1994/1995) double dose (week 0, 3)</td>
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<td>A/H3N2: 4/5 (80%)</td>
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<td>TIV (1994/1995) double dose (week 0, 3)</td>
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<td>Fraud</td>
<td>1999</td>
<td>pc HTX, A</td>
<td>A/H1N1: 79/79(100%)</td>
<td>106/109 (97.2%)</td>
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<td>A/H3N2: 55/79 (69.3%)</td>
<td>104/109 (95.4%)</td>
<td>TIV (1996/97), single dose</td>
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<td>Burbach</td>
<td>1999</td>
<td>pc LTX, A</td>
<td>A/H1N1: 57/63 (92%)</td>
<td>57/59 (97%)</td>
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<td>A/H3N2: 57/63 (92%)</td>
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<td>Kimball</td>
<td>2000</td>
<td>pc HTX, A</td>
<td>Overall: 12/29 (41%)</td>
<td>4/5 (90%)</td>
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<td>Sanchez-Fructuoso</td>
<td>2000</td>
<td>pc RTX, A</td>
<td>A: 23/49 (46.2%)</td>
<td>26/37 (69%)</td>
<td>TIV (1997/98), single dose</td>
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<td>B: 10/49 (20.5%)</td>
<td>17/37 (44.8%)</td>
<td>TIV (1997/98), single dose</td>
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<td>Soesman</td>
<td>2000</td>
<td>pc LTX, A</td>
<td>A/H1N1: 53/60 (88.3%)</td>
<td>44/45 (97.8%)</td>
<td>TIV (1997/98), double dose (week 0, 4)</td>
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<td>A/H3N2: 56/60 (93.3%)</td>
<td>45/45 (100%)</td>
<td>TIV (1997/98), double dose (week 0, 4)</td>
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<td>B: 48/60 (80%)</td>
<td>36/45 (81.1%)</td>
<td>TIV (1997/98), double dose (week 0, 4)</td>
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## Table 3. Cont.

### Category C: Influenza

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<tr>
<th>First author</th>
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<th>Patients</th>
<th>Short-term response SOT (%)</th>
<th>Short-term response HC (%)</th>
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<tr>
<td>Kimball</td>
<td>2001</td>
<td>pc</td>
<td>HTX, A</td>
<td>Overall: 12/29 (41%)</td>
<td>NN (80%)</td>
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<td>Mazzone</td>
<td>2001</td>
<td>pc</td>
<td>PTX, A</td>
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<td>15/21 (71%)</td>
<td>TIV (1999/2000), single dose</td>
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<td>A/H3N2: 17/43 (40%)</td>
<td>20/21 (95%)</td>
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<td>B: 4/43 (19%)</td>
<td>10/21 (48%)</td>
<td>TIV (1999/2000), single dose</td>
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<td>A/H3N2: 3/15 (15%)</td>
<td>8/9 (89%)</td>
<td>TIV (1999/2000), single dose</td>
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<td></td>
<td>B: 6/20 (30%)</td>
<td>5/9 (56%)</td>
<td>TIV (1999/2000), single dose</td>
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<td>Wyczgal</td>
<td>2002</td>
<td>pu</td>
<td>RTX, A</td>
<td>Overall: NN/23 (86.7–100%)</td>
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<td>TIV (1999/2000), single dose</td>
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<td>Cavdar</td>
<td>2003</td>
<td>pc</td>
<td>RTX, A</td>
<td>A/H1N1: 13/17 (76%)</td>
<td>9/10 (90%)</td>
<td>TIV (1997/98), single dose</td>
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<td>A/H3N2: 13/17 (76%)</td>
<td>10/10 (100%)</td>
<td>TIV (1997/98), single dose</td>
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<td>B: 1/17 (100%)</td>
<td>10/10 (100%)</td>
<td>TIV (1997/98), single dose</td>
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<td>Lawal</td>
<td>2004</td>
<td>pu</td>
<td>LTX, A</td>
<td>A/H1N1: 37/51 (73%)</td>
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<td>TIV (2002/03), single dose</td>
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<td>A/H3N2: 35/51 (69%)</td>
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<td>B: 2/51 (43%)</td>
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<td>TIV (2002/03), single dose</td>
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<tr>
<td>Hayney</td>
<td>2004</td>
<td>pc</td>
<td>PTX, A</td>
<td>Overall: 29/64 (46%)</td>
<td>22/35 (63%)</td>
<td>TIV (2002/03), single dose</td>
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<td>Ballet a)</td>
<td>2006</td>
<td>pc</td>
<td>RTX, A</td>
<td>Overall: 0/6 (0%)</td>
<td>7/9 (78%)</td>
<td>TIV (2003/04), single dose</td>
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<td>pc</td>
<td>RTX, A</td>
<td>Overall: 1/9 (11%)</td>
<td>9/15 (60%)</td>
<td>TIV (2004/05), single dose</td>
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<tr>
<td>Willcocks a)</td>
<td>2006</td>
<td>ra</td>
<td>RTX, LTX, A</td>
<td>A/H1N1: 7/16 (44%)</td>
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<td>TIV (2004/05), single dose</td>
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<td>A/H3N2: 13/16 (81%)</td>
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<td>TIV (2004/05), single dose</td>
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<td>B: 7/16 (44%)</td>
<td>–</td>
<td>TIV (2004/05), single dose</td>
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<tr>
<td>Willcocks b)</td>
<td>2006</td>
<td>ra</td>
<td>RTX, LTX, A</td>
<td>A/H1N1: 11/15 (73%)</td>
<td>–</td>
<td>TIV (2004/05), single dose</td>
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<td>A/H3N2: 15/15 (100%)</td>
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<td>TIV (2004/05), single dose</td>
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<td>B: 10/15 (67%)</td>
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<td>TIV (2004/05), single dose</td>
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<td>Keshtkar-Jahromi a)</td>
<td>2008</td>
<td>pc</td>
<td>RTX, A</td>
<td>A/H1N1: 10/16 (62.5%)</td>
<td>38/40 (93%)</td>
<td>TIV (2006/07), single dose</td>
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<td>A/H3N2: 14/16 (87.5%)</td>
<td>37/40 (92.5%)</td>
<td>TIV (2006/07), single dose</td>
</tr>
<tr>
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<td>B: 14/16 (87.5%)</td>
<td>39/40 (97.5%)</td>
<td>TIV (2006/07), single dose</td>
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<tr>
<td>Keshtkar-Jahromi b)</td>
<td>2008</td>
<td>pc</td>
<td>RTX, A</td>
<td>A/H1N1: 22/24 (91.7%)</td>
<td>38/40 (95%)</td>
<td>TIV (2006/07), single dose</td>
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<td>A/H3N2: 21/24 (87.5%)</td>
<td>37/40 (92.5%)</td>
<td>TIV (2006/07), single dose</td>
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<td>B: 24/24 (100%)</td>
<td>39/40 (97.5%)</td>
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<td>Scharpe 11</td>
<td>2008</td>
<td>pc</td>
<td>RTX, A</td>
<td>A/H1N1: 153/165 (92.7%)</td>
<td>29/41 (70.7%)</td>
<td>TIV (2003/04), single or double dose</td>
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<td>A/H3N2: 130/165 (78.7%)</td>
<td>34/41 (82.9%)</td>
<td>TIV (2003/04), single or double dose</td>
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<td>B: 137/165 (82.9%)</td>
<td>20/41 (48.8%)</td>
<td>TIV (2003/04), single or double dose</td>
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<td>Gaeta</td>
<td>2009</td>
<td>pu</td>
<td>LTX, A</td>
<td>A/H1N1: 8/16 (50%)</td>
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<td>TIV (2007/08), single dose</td>
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<td>A/H3N2: 9/16 (56.3%)</td>
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<td>TIV (2007/08), single dose</td>
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</table>
### Category C: Influenza

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Design</th>
<th>Patients</th>
<th>Short-term response SOT (%)</th>
<th>Short-term response HC (%)</th>
<th>Vaccine (Season), Vaccination scheme</th>
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<tbody>
<tr>
<td>Evison a)</td>
<td>2009</td>
<td>ra</td>
<td>RTX, A</td>
<td>Overall: 30/37 (81.1%)</td>
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<td>TV (2005/06), single dose</td>
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<tr>
<td>Evison b)</td>
<td>2009</td>
<td>ra</td>
<td>RTX, A</td>
<td>Overall: 33/37 (89.2%)</td>
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<td>TV (2005/06), single dose</td>
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<td>Birdwell</td>
<td>2009</td>
<td>pc</td>
<td>RTX, A</td>
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<td>88/106 (83%)</td>
<td>TV (2005/2006), single dose</td>
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<td>A/H3N2: 37/53 (69.8%)</td>
<td>97/106 (91.5%)</td>
<td>TV (2005/2006), single dose</td>
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<td>Salles</td>
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<td>RTX, A</td>
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<td>TV (2004/2005), single dose</td>
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<td>A/H3N2: 25/69 (36.3%)</td>
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<td>Candon</td>
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<td>pc</td>
<td>RTX, A</td>
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<td>11/19 (57.9%)</td>
<td>TV (2005/2006), single dose</td>
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<td>A/H3N2: 13/65 (21.5%)</td>
<td>11/19 (57.9%)</td>
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<td>LTX, P</td>
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<td>5/19 (26.3%)</td>
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<td>A/H3N2: 1/7 (14%)</td>
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<td>pc</td>
<td>LTX, P</td>
<td>A/H1N1: 6/13 (46%)</td>
<td>26/63 (42%)</td>
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<td>A/H3N2: 4/13 (31%)</td>
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<td>A/H1N1: 6/13 (46%)</td>
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<td>A/H3N2: 4/13 (31%)</td>
<td>10/63 (16%)</td>
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<td>A/H3N2: 7/17 (42.2%)</td>
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<td>Hojsak b)</td>
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<td>A/H1N1: 20/37 (54%)</td>
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<td>TV (2005/06) double dose</td>
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<td>A/H3N2: 21/37 (56.7%)</td>
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<td>TV (2005/06) double dose</td>
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<td>Nailescu</td>
<td>2011</td>
<td>pc</td>
<td>RTX, P</td>
<td>A/H1N1: 29/66 (43.9%)</td>
<td>20/21 (95.2%)</td>
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<td>12/21 (57.1%)</td>
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### Category D: Streptococcus pneumoniae

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<th>Short-term response HC (%)</th>
<th>Long-term response SOT</th>
<th>Vaccine, Vaccination scheme</th>
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<td>Fuchshuber</td>
<td>1996</td>
<td>pu</td>
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<td>6/7 (86%)</td>
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<td>3/7 (43%)</td>
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<td>Year</td>
<td>Design</td>
<td>Patients</td>
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<td>Short-term response</td>
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<td>1/15 (94%)</td>
<td>2/23 (100%)</td>
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<td>Gannery a) 1998</td>
<td>pu</td>
<td>RTX, A</td>
<td>2/12 (100%)</td>
<td>2/23 (100%)</td>
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<td>Kazanciouglu 2000</td>
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<td>3/35 (94%)</td>
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<td>-</td>
<td>N/35 (N%)</td>
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<td>pc</td>
<td>HTX, A</td>
<td>32/35 (91%)</td>
<td>9,10 N/35 (66.6%)</td>
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<td>21/21 (100%)</td>
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<td>25/30 (83.3%)</td>
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<td>RTX, A</td>
<td>22/30 (73.3%)</td>
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<td>Blumberg 2009</td>
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<td>RTX, A</td>
<td>23/23 (100%)</td>
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<td>Barton a) 2009</td>
<td>pu</td>
<td>RTX, A</td>
<td>14/15 (93.3%)</td>
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<td>PCV7, single dose</td>
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<td>RTX, A</td>
<td>25/30 (83.3%)</td>
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<td>-</td>
<td>PCV7, single dose</td>
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</tr>
<tr>
<td>Barton c) 2011</td>
<td>pu</td>
<td>RTX, A</td>
<td>22/30 (73.3%)</td>
<td>-</td>
<td>-</td>
<td>PCV7, single dose</td>
<td></td>
</tr>
<tr>
<td>Barton d) 2011</td>
<td>pu</td>
<td>RTX, A</td>
<td>16/35 (53.3%)</td>
<td>-</td>
<td>-</td>
<td>PCV7, single dose</td>
<td></td>
</tr>
<tr>
<td>Gattringer a) 2011</td>
<td>pu</td>
<td>RTX, A</td>
<td>13/15 (94%)</td>
<td>-</td>
<td>-</td>
<td>PCV7, single dose</td>
<td></td>
</tr>
<tr>
<td>Gattringer b) 2011</td>
<td>pu</td>
<td>RTX, A</td>
<td>25/30 (83.3%)</td>
<td>-</td>
<td>-</td>
<td>PCV7, single dose</td>
<td></td>
</tr>
<tr>
<td>Category D: Haemophilus influenzae</td>
<td>First author</td>
<td>Year</td>
<td>Design</td>
<td>Patients</td>
<td>Short-term response</td>
<td>SOT (%)</td>
<td>Short-term response</td>
</tr>
<tr>
<td>Sever 1999 pu RTX, P</td>
<td>24/30 (80%)</td>
<td>-</td>
<td>-</td>
<td>Single dose conjugate HibV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sever 2011 pu RTX, P</td>
<td>24/30 (80%)</td>
<td>-</td>
<td>-</td>
<td>Single dose conjugate HibV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category D: Neisseria meningitides</td>
<td>First author</td>
<td>Year</td>
<td>Design</td>
<td>Patients</td>
<td>Short-term response</td>
<td>SOT (%)</td>
<td>Short-term response</td>
</tr>
<tr>
<td>Zlamy 2011 p RTX, LTX, P</td>
<td>8/8 (100%)</td>
<td>-</td>
<td>-</td>
<td>Men C vaccine conjugated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category E: Varicella</td>
<td>First author</td>
<td>Year</td>
<td>Design</td>
<td>Patients</td>
<td>Short-term response</td>
<td>SOT (%)</td>
<td>Short-term response</td>
</tr>
<tr>
<td>Zamora 1994 pu RTX, P</td>
<td>11/17 (64.7%)</td>
<td>-</td>
<td>-</td>
<td>Primary vaccination before SOT, post-transplant single dose (booster)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kano 2002 pu RTX, P</td>
<td>5/7 (71%)</td>
<td>-</td>
<td>-</td>
<td>Single or double (0, 1–2 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chaves 2005 pu RTX, P</td>
<td>4/7 (66%)</td>
<td>-</td>
<td>-</td>
<td>Single dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weinberg 2006 pu LTX, P</td>
<td>10/15 (80%)</td>
<td>-</td>
<td>-</td>
<td>Single dose</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 3. Cont.

#### Category E: Varicella

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Design</th>
<th>Patients</th>
<th>Short-term response SOT (%)</th>
<th>Short-term response HC (%)</th>
<th>Long-term response SOT</th>
<th>Vaccine, Vaccination scheme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khan a)</td>
<td>2006</td>
<td>r</td>
<td>LTX, P</td>
<td>20/31 (64.5%)</td>
<td>–</td>
<td>–</td>
<td>Single or multiple VZVV</td>
</tr>
<tr>
<td>Shinjoh a)</td>
<td>2008</td>
<td>pu</td>
<td>RTX, P</td>
<td>9/11 (82%)</td>
<td>–</td>
<td>–</td>
<td>Single or multiple vaccination</td>
</tr>
</tbody>
</table>

#### Category E: Mumps, Measles, Rubella

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Design</th>
<th>Patients</th>
<th>Short-term response SOT (%)</th>
<th>Short-term response HC (%)</th>
<th>Long-term response SOT</th>
<th>Vaccine, Vaccination scheme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rand</td>
<td>1993</td>
<td>r</td>
<td>LTX, P</td>
<td>7/18 (39%)</td>
<td>–</td>
<td>–</td>
<td>NA</td>
</tr>
<tr>
<td>Kano a)</td>
<td>2002</td>
<td>pc</td>
<td>LTX, P</td>
<td>11/13 (85%)</td>
<td>–</td>
<td>–</td>
<td>Primary vaccination before SOT, post-transplant single dose (booster)</td>
</tr>
<tr>
<td>Kano b)</td>
<td>2002</td>
<td>pc</td>
<td>LTX, P</td>
<td>2/2 (100%)</td>
<td>–</td>
<td>–</td>
<td>Primary vaccination before SOT, post-transplant single dose (booster)</td>
</tr>
<tr>
<td>Kano c)</td>
<td>2002</td>
<td>pc</td>
<td>LTX, P</td>
<td>6/6 (100%)</td>
<td>–</td>
<td>–</td>
<td>Primary vaccination before SOT, post-transplant single dose (booster)</td>
</tr>
<tr>
<td>Khan b)</td>
<td>2006</td>
<td>r</td>
<td>LTX, P</td>
<td>19/26 (73%)</td>
<td>–</td>
<td>–</td>
<td>Single or multiple doses MMR</td>
</tr>
<tr>
<td>Shinjoh b)</td>
<td>2008</td>
<td>pu</td>
<td>LTX, P</td>
<td>9/11 (82%)</td>
<td>–</td>
<td>–</td>
<td>Single or multiple doses MMR</td>
</tr>
<tr>
<td>Shinjoh c)</td>
<td>2008</td>
<td>pu</td>
<td>LTX, P</td>
<td>15/15 (100%)</td>
<td>–</td>
<td>–</td>
<td>Single or multiple doses MMR</td>
</tr>
</tbody>
</table>

#### Category F: Tick-borne encephalitis

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Design</th>
<th>Patients</th>
<th>Short-term response SOT (%)</th>
<th>Short-term response HC (%)</th>
<th>Long-term response SOT</th>
<th>Vaccine, Vaccination scheme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengler</td>
<td>1999</td>
<td>pc</td>
<td>HTX, A</td>
<td>11/31 (35.5%)</td>
<td>29/29 (100%)</td>
<td>–</td>
<td>0, 1, 3 weeks, TBEV</td>
</tr>
</tbody>
</table>

#### Category F: Rabies

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Design</th>
<th>Patients</th>
<th>Short-term response SOT (%)</th>
<th>Short-term response HC (%)</th>
<th>Long-term response SOT</th>
<th>Vaccine, Vaccination scheme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cramer²⁹</td>
<td>2008</td>
<td>r</td>
<td>LTX, RTX, P</td>
<td>7/8 (87.5%)</td>
<td>–</td>
<td>5/5 (100%)</td>
<td>Active (day 0, 3, 7, 14, 28) RVV combined with passive immunization</td>
</tr>
<tr>
<td>Rodriguez-Romo³⁰</td>
<td>2011</td>
<td>c</td>
<td>RTX, A</td>
<td>1/1</td>
<td>–</td>
<td>1/1</td>
<td>Active (day 0, 3, 7, 14, 28, 38, 41, 45, 52, 66) RVV combined with passive immunization</td>
</tr>
</tbody>
</table>

In the column “Short-term response SOT” is the number of patients given that had a positive response >2 weeks and ≤3 months after the last vaccination while in the column “Long-term response SOT” the number of patients that kept a positive response after ≥12 months is given (exceptions are marked with number). Data presented as number of patients with vaccination response/total number of patients.


1 patients receiving a chimeric monoclonal antibody against CD20.
2 patients receiving conventional immunosuppressive medication.
3 after 1st dose, controls received a different vaccination scheme compared to SOT recipients (one vs. two doses of vaccine, respectively).
Table 3. Cont.

4 after 2nd dose, controls received a different vaccination scheme compared to SOT recipients (one vs. two doses of vaccine, respectively).
5 after 3rd dose, controls received a different vaccination scheme compared to SOT recipients (one vs. two doses of vaccine, respectively).
6 patients were randomized to vaccine vs. no vaccine for the purpose of studying rejection.
7 patients receiving calcineurin-inhibitors.
8 patients receiving sirolimus.
9 patients receiving mycophenolate mofetil.
10 patients receiving azathioprin.
11 SOT recipients received either one or two doses of vaccine, however data for the double-dose trial are not given and stated that no difference to the single dose trial.
12 Subunit vaccine.
13 Virosomal vaccine.
14 For controls exact numbers were not given but stated that no difference between patients and controls.
15 Response measured by enzyme-linked immunoassay (ELISA).
16 Response measured by opsoophagization assay (OPA).
17 Response measured by enzyme-linked immunoassay (ELISA).
18 Response measured by opsoophagization assay (OPA).
19 Long-term response of PPV 23 vs. PCV7 by follow up of the cohort by Kumar et al. 2003, mean continued response from patients initially vaccinated against PPV23 from varying patient numbers ranging from 2 to 10 patients.
20 Long-term response of PPV 23 vs. PCV7 by follow up of the cohort by Kumar et al. 2003, mean continued response of patients initially vaccinated against PCV7 from varying patient numbers ranging from 4 to 11 patients.
21 Mean response after PCV7 only to serotypes 4, 6B, 9V, 14, 18C, 19F, 23F.
22 Mean response after PCV7 followed by PPV23 to serotype 1, 5 und 7F after additional PP23 vaccination in the cohort from 23.
23 Response to measles component.
24 Response to mumps component.
25 Response to rubella component.
26 Response to mumps component.
27 Response to measles component.
28 Response to rubella component.
29 Long-term response was accepted as 6 months after vaccination.
30 Adequate response was seen but which decreased rapidly.

doi:10.1371/journal.pone.0056974.t003
patient cohorts. Of the five randomized trials, three randomized to the type of vaccine used (two for pneumococcal conjugate vaccine vs. polysaccharide vaccine [11,12] and one for influenza vaccine subunit vs. virosomal vaccine [13]), one trial on influenza vaccination was randomized for the immunosuppressive regimen (calcineurin-inhibitor vs. sirolimus [14]) and one trial which primarily observed graft rejection was randomized to intervention (single dose influenza vaccination vs. no vaccination [15]). In total, 65 trials were investigating inactivated vaccines in both adults and children and seven trials investigated live attenuated vaccines solely in paediatric SOT recipients. Inclusion of a control group was highly variable with control groups entirely missing for HBV and for live vaccines. At the opposite end the majority of influenza vaccine trials had control groups.

Numbers of SOT recipients vaccinated ranged from 1 to 165 and healthy control numbers ranged from 7 to 109. There were 47 trials on vaccination of adult SOT and 25 of paediatric SOT recipients. Most trials included renal transplant recipients (RTX, 31 articles), followed by liver transplant (LTX, 18 articles), heart transplant (HTX, 11 articles), lung transplant (PTX, 2 articles) or mixed cohorts of organ transplant recipients (9 articles). Of the vaccines studied, inactivated influenza vaccination was the most common (36 articles), followed by vaccination against *Streptococcus pneumoniae* (9 articles), hepatitis B (7 articles), tetanus (6 articles), varicella (6 articles), diphtheria (4 articles), mumps, measles, rubella (4 articles), hepatitis A (3 articles), vaccination against *Haemophilus influenzae* (2 articles), rabies vaccine (2 article), polio (1 article), *Neisseria meningitides* (1 article) and tick-borne encephalitis vaccine (1 article). Some studies investigated more than one vaccine in the same cohort. No studies were found on *Bordetella pertussis*, rotavirus, human papilloma virus vaccines or vaccines recommended for certain geographic areas ("travel vaccines" such as Japanese encephalitis vaccines) apart from tick-borne encephalitis vaccine and rabies.

Most trials only assessed the short-term response within two weeks to three months after vaccination. Only a few also measured long-term responses at a second time point. Data on long-term response were not always extractable for all SOT recipients with a positive response at first assessment after vaccination. Most trials, despite small patient numbers, addressed vaccine safety issues. None of the trials neither on inactivated or on live vaccines, however, reported severe adverse events (SAEs) or transplant-related complication such as organ rejection after vaccination during the time period of the trial.

**Short-term Response**

**Tetanus.** We retrieved six trials investigating the response to tetanus toxoid vaccination in SOT recipients with publication dates ranging from 1995 to 2010 (Table 3, category A) [16–21]. Four trials were prospective uncontrolled and two prospective controlled. All trials assessed the short-term response; two trials additionally assessed the long-term response [17,20]. Three trials included adult SOT recipients and three trials paediatric SOT recipients. All trials were performed only on RTX recipients. Patient numbers ranged from 7 to 150 in SOT recipients and 13 to 96 in the control group.

In five of six studies high response rates ranging from of 85%–100% were seen [16–20] with no significant difference in the response rates of SOT recipients and healthy controls in controlled trials [16,18]. Response rates were lower in the study by Puissant-Lubrano et al., which compared conventional immunosuppression to immunosuppression with an anti-CD20 monoclonal antibody (61.5% vs. 30.6%, respectively) (Table 3, category A) [21].

Overall, vaccination with tetanus toxoid in the post-transplant period elicits a high rate of responders in SOT recipients with conventional immunosuppression with no significant difference to healthy controls (p = 0.96 on only two studies) while immunosuppression with anti-CD20 monoclonal antibody showed a decreased response rate compared to conventional immunosuppressive medication (p = 0.043 in meta-regression) (Table 3 and Figure 2, category A).

**Diphtheria.** Four trials were identified with SOT recipients vaccinated against diphtheria with publication dates ranging from
1997 to 1999 (Table 3, category A) [17–20]. Three trials were prospective uncontrolled while one trial was prospective controlled. Three trials were performed on paediatric SOT recipients, one trial assessed adult SOT recipients, and all were RTX recipients. Patient numbers ranged from 33 to 164 SOT recipients; the controlled trial had 106 controls.

Short-term response rates ranged from 88.5% to 95% with comparable response rates in SOT recipients and controls (88.5% vs. 96.2%, respectively) [17,18]. All studies with diphtheria vaccination in the post-transplant phase show comparable high response rates (I-squared = 0%).

**Polio.** Only one trial with an inactivated polio vaccine (IPV) in SOT recipients was identified published in 1997 (Table 2, category A) [18]. Short-term response rate in this prospective controlled cohort of adult RTX recipients was 91.6% compared to 97.9% in controls, which shows high response for polio vaccine in the post-transplant era with no significant difference to controls (p = 0.125 based on own calculations) (see Table 3, group A).

**Hepatitis A.** Three trials on hepatitis A (HAV) vaccination in SOT recipients were included with publication dates ranging from 1999 to 2001 (Table 3, category B) [22–24]. All trials were in adult recipients of either liver or kidney grafts. The trials addressed primary immunization schemes with two successive vaccine doses. Patient numbers ranged from 8 to 39 SOT recipients; the controlled trial had 27 controls. Maximal response rates after two vaccinations ranged from 0% [22], which in contrast applied a vaccination scheme with month 0 and 2 compared to all other trial with month 0 and 6, to 26% in one study [24] and 97.4% in LTX recipients and 71.8% in RTX recipients compared to 100% response in controls [23]. Overall, results for HAV vaccination show a high degree of heterogeneity (I-squared = 97.7%). While one study shows high response rates for both RTX and LTX, others did not confirm this finding (Figure 2, category B).

**Hepatitis B.** We identified seven trials on hepatitis B vaccination after SOT with publication dates ranging from 1992 to 2001 (Table 3, category B) [25–31]. Six trials were prospective uncontrolled while one trial was retrospective. None of the trials had a control group. Five trials were performed in LTX recipients with three in a paediatric and two in an adult LTX cohort, one...
A trial was conducted on adult heart- and one on adult kidney transplant recipients, respectively. Patient numbers ranged from 4 to 86 SOT recipients. Most trials applied a multi dose scheme. In adult SOT recipients, the response rate was low ranging from 6.7% to 36% while in contrast, a high response rate was seen in the paediatric trials ranging from 63.6% to 100% (Figure 2, category B) [29–31]. Overall, response rate to HBV after transplantation in adult SOT recipients is poor while in paediatric SOT recipients a 58% (95 CI: 37%–80%) higher response rate was seen (p = 0.001 from meta-regression).

Category C: Vaccination against seasonal influenza.

In total, 36 trials on inactivated trivalent influenza vaccination after SOT were included in the review with publication dates ranging from 1980 to 2011 and vaccines against the circulating strains of the influenza season of 1981/82 to 2007/2008 [13–15,32–64].

In nine trials a prospective uncontrolled trial design was used while 25 were prospective controlled, one trial was retrospective. Three RCT were identified which were randomized to the number of vaccine doses applied [15], to the type of immunosuppressive medication [14] and the vaccine type used [13]. Some trials applied more than one study design within one publication. Six trials investigated response in paediatric SOT recipients. Patient numbers ranged from 5 to 165 for SOT recipients and from 5 to 109 for controls. Most trials were on RTX recipients (n = 19), followed by LTX (n = 11), HTX (n = 9) and PTX (n = 3) recipients.

Vaccination response was in most trials investigated as the response to each of the three components A/H1N1, A/H3N2 and B (Figure 3, 4, 5), while others only observed overall response to influenza A or B or only total overall response (the latter two type of trials are not displayed in a figure). The most common applied vaccination scheme was single dose while some trials investigated a double or even triple dose scheme of the same vaccine, however in several controlled trials the control group received a different vaccination scheme than SOT recipients (single vs. multi dose regimen, respectively). Conflicting results were found for multiple versus single dose vaccination in SOT recipients. While some trials revealed an increased response rate after multiple dose vaccination in SOT recipients, in other trials this was less clear. Furthermore, the multiple dose regimen was not applied in most control groups. None of the trials assessed long-term vaccination responses.

In the trials comparing different immunosuppressive drugs, calcineurin-inhibitors and azathioprin were associated with a slightly better response compared to sirolimus and mycophenolate mofetil (Figure 3, 4, 5) [14,56].

Overall, variability of the response was very high and ranged from 0–100% in SOT recipients with corresponding high values of I-squared (all larger than 92%) (Figure 3, 4, 5). When comparing response rate of SOT recipients with controls, several studies...
showed a clear trend to a less pronounced response in SOT recipients with overall a 10% to 16% lower response rate in SOT recipients (Figure 6, 7, 8). The difference in response to control patients was in renal and lung transplant recipients less pronounced than in the other SOT groups. In some studies, however, the response rate in SOT recipients was even higher than in controls. Almost all trials, however, observed a measurable vaccine response at least in a subset of SOT recipients after single dose vaccination with a trend to lower response rates in SOT recipients compared to healthy controls in most of the trials.

Category D: Vaccination against bacterial pathogens.

**Streptococcus pneumonia.** Nine studies were identified which investigated pneumococcal vaccine in SOT recipients with publication dates ranging from 1998 to 2011 (Table 3, category D) [11,12,42,65–70].

The trial design was prospective uncontrolled in five trials, and prospective controlled in two trials. Two RCTs were randomized to the type of vaccine given. Three trials were on paediatric and five on adult SOT recipients. There were trials on SOT recipients of kidney (3 trials), heart (3 trials), and three trials on mixed cohorts.

In four trials responses to a randomized or mixed vaccination scheme with both types of vaccines were investigated. Overall response ranged from 32% to 100% with comparable responses in the control group, if included [42,68]. Response rate was assessed either as response to at least one serotype from a group of representative antigens or an overall or mean response to selected antigens. Those antigens selected as “representative” varied between trials. Response rate in all studies was above 50% with a summary estimate of 83% (95% CI: 83%–93%) with substantial heterogeneity (I-squared = 81%) (Figure 2, category D).

**Haemophilus influenzae (Hib).** We retrieved two prospective trials on Hib vaccination in SOT recipients published in 1998 and 1999, one prospective controlled in RTX and one prospective uncontrolled in HTX recipients (Table 3, category D) [66,71]. The vaccination responses were 56% in adult RTX recipients compared to 71% in controls [71] and 85% in paediatric HTX recipients [66] one month after vaccination with Hib conjugate vaccine. Long-term responses were not assessed. An acceptable response rate above 50% in SOT recipients in both studies was observed (Figure 2, category D).

**Neisseria meningitides.** We retrieved one study which investigated vaccination with conjugated meningitis C vaccine in a mixed cohort of paediatric SOT recipients [72]. A positive short-term response after 3 months was seen in all patients (Figure 2, category D), however the authors stated that titers waned rapidly.

Category E: Vaccination with attenuated live virus vaccines.

**Varicella.** Six trials on live-attenuated varicella vaccination after SOT were identified with publication dates ranging from 1994 to 2008 (Table 5, category E) [73–78]. Five were prospective
uncontrolled and one was retrospective. All trials were conducted in paediatric SOT recipients with three trials on RTX recipients, [73,74,76] two trials on LTX [77] and one trial on a mixed cohort of recipients of liver or intestine grafts [75]. Short-term response rates ranged from 64.5% to 87%. Acceptable response rates were observed in all studies with an overall estimate of 73% (95% CI: 64%–83%) with little heterogeneity (I-squared = 0%) in SOT recipients after post-transplantation vaccination are seen (Figure 2, category E).

Mumps, measles and rubella. Four trials on mumps, measles and rubella vaccination in SOT recipients were identified with publication dates ranging from 1993 to 2008 [74,77–79]. Two trials were retrospective and one prospective uncontrolled, none of the trials assessed long-term responses. Only two trials specified the immune response to the individual components of the vaccine. Overall, all trials had small patient numbers ranging from 6 to 26 SOT recipients with a vaccination response ranging from 39% to 100%. In the two larger retrospective studies by Khan et al. and Rand et al., which observed response rates over a time period of 15 months and 5 years, respectively, lower response rates were observed. In the trial by Shinjoh et al., high response rates in a very small patient number was seen with a lower response rate to the mumps component of the vaccine (Table 2, category E).

Overall, the observed positive response rates were above 70% in all but one study conducted in 1993 resulting in a summary estimate of 85% (95% CI: 72%–99%) with substantial heterogeneity (I-squared = 76%) (Figure 2, category E). Omitting the 1993 study reduced heterogeneity substantially (I-squared = 36%).

Category F: Vaccines indicated in certain geographical areas.

Tick-borne encephalitis. One trial was included that measured vaccination response after TBE vaccination, published in 1999 (Table 3, category F) [80]. In this prospective controlled trial, TBE vaccination in an endemic area in Germany was studied in 31 HTX recipients. SOT recipients responded in 35.5%, controls in 100% (Figure 2, category F).

Rabies. Two trials were found that assessed immune response to rabies vaccine in SOT recipients which were exceptionally included despite not meeting all inclusion criteria [81,82] and despite the fact that in both trials active and passive vaccination was performed, due to the global relevance of rabies and the importance to know the response of SOT recipients to standard post-exposure vaccination as the only remedy after a potential risk contact (Table 3, category F). Vaccination response to the post-exposure vaccination scheme was analysed in an uncontrolled retrospective trial in 8 paediatric SOT recipients [82] and in an adult kidney transplant patient [81]. In the study by Cramer et al., the short-term response was 87.5% and in a 6 months assessment, anti-rabies antibodies were found in 100% of SOT recipients. Because of the relevance of this finding, we exceptionally included the 6-month response into our analysis. In contrast, the case report

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**Figure 5. Forest plot for short-term response for vaccine category C (influenza) against influenza B.** All type of trials which assessed specific response to B are included. Numbers in brackets refer to legend in Table 3. doi:10.1371/journal.pone.0056974.g005

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<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Transplant type</th>
<th>Proportion with positive outcome (95% CI)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adron et al. a)</td>
<td>1997</td>
<td>HTX</td>
<td>0.08 (0.01, 0.36)</td>
<td>25</td>
</tr>
<tr>
<td>Adron et al. b)</td>
<td>1997</td>
<td>HTX</td>
<td>0.12 (0.01, 0.36)</td>
<td>17</td>
</tr>
<tr>
<td>Adron et al. c)</td>
<td>1997</td>
<td>HTX</td>
<td>0.29 (0.10, 0.56)</td>
<td>17</td>
</tr>
<tr>
<td>Dengler et al. a)</td>
<td>1998</td>
<td>HTX</td>
<td>0.38 (0.15, 0.65)</td>
<td>16</td>
</tr>
<tr>
<td>Blumberg et al. a)</td>
<td>1999</td>
<td>HTX</td>
<td>0.56 (0.21, 0.86)</td>
<td>9</td>
</tr>
<tr>
<td>Blumberg et al. b)</td>
<td>1999</td>
<td>HTX</td>
<td>0.96 (0.49, 1.00)</td>
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</tr>
<tr>
<td>Freudent et al.</td>
<td>1999</td>
<td>HTX</td>
<td>0.52 (0.22, 0.43)</td>
<td>79</td>
</tr>
<tr>
<td>Mack et al.</td>
<td>1999</td>
<td>LTX</td>
<td>0.56 (0.40, 0.72)</td>
<td>39</td>
</tr>
<tr>
<td>Burle et al.</td>
<td>2000</td>
<td>LTX</td>
<td>0.80 (0.68, 0.89)</td>
<td>60</td>
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<tr>
<td>Duchini et al.</td>
<td>2001</td>
<td>LTX</td>
<td>0.30 (0.12, 0.59)</td>
<td>20</td>
</tr>
<tr>
<td>Lavel et al.</td>
<td>2004</td>
<td>LTX</td>
<td>0.43 (0.20, 0.60)</td>
<td>51</td>
</tr>
<tr>
<td>Gerds et al.</td>
<td>2006</td>
<td>LTX</td>
<td>0.39 (0.15, 0.63)</td>
<td>16</td>
</tr>
<tr>
<td>Gotz et al. a)</td>
<td>2010</td>
<td>LTX</td>
<td>0.14 (0.00, 0.58)</td>
<td>7</td>
</tr>
<tr>
<td>Gotz et al. b)</td>
<td>2010</td>
<td>LTX</td>
<td>0.23 (0.05, 0.64)</td>
<td>13</td>
</tr>
<tr>
<td>Gotz et al. c)</td>
<td>2010</td>
<td>LTX</td>
<td>0.15 (0.02, 0.45)</td>
<td>13</td>
</tr>
<tr>
<td>Hojda et al. a)</td>
<td>2011</td>
<td>LTX</td>
<td>0.17 (0.04, 0.34)</td>
<td>18</td>
</tr>
<tr>
<td>Hojda et al. b)</td>
<td>2011</td>
<td>LTX</td>
<td>0.43 (0.32, 0.66)</td>
<td>37</td>
</tr>
<tr>
<td>Maccone et al.</td>
<td>2005</td>
<td>RTX</td>
<td>0.05 (0.03, 0.22)</td>
<td>43</td>
</tr>
<tr>
<td>Brigger et al.</td>
<td>1986</td>
<td>RTX</td>
<td>0.10 (0.07, 0.13)</td>
<td>13</td>
</tr>
<tr>
<td>Goktas et al.</td>
<td>1993</td>
<td>RTX</td>
<td>0.43 (0.31, 0.66)</td>
<td>33</td>
</tr>
<tr>
<td>Firth et al.</td>
<td>1995</td>
<td>RTX</td>
<td>0.76 (0.50, 0.93)</td>
<td>17</td>
</tr>
<tr>
<td>Cander et al.</td>
<td>2003</td>
<td>RTX</td>
<td>1.00 (0.80, 1.00)</td>
<td>17</td>
</tr>
<tr>
<td>Keilhaber-Jahromi et al. a)</td>
<td>2008</td>
<td>RTX</td>
<td>0.88 (0.62, 0.98)</td>
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</tr>
<tr>
<td>Keilhaber-Jahromi et al. b)</td>
<td>2008</td>
<td>RTX</td>
<td>1.00 (0.86, 1.00)</td>
<td>34</td>
</tr>
<tr>
<td>Scarpaci et al.</td>
<td>2008</td>
<td>RTX</td>
<td>0.63 (0.59, 0.74)</td>
<td>165</td>
</tr>
<tr>
<td>Birkett et al.</td>
<td>2009</td>
<td>RTX</td>
<td>0.67 (0.57, 0.78)</td>
<td>53</td>
</tr>
<tr>
<td>Salles et al.</td>
<td>2009</td>
<td>RTX</td>
<td>0.06 (0.00, 0.25)</td>
<td>69</td>
</tr>
<tr>
<td>Candon et al.</td>
<td>2009</td>
<td>RTX</td>
<td>0.20 (0.11, 0.31)</td>
<td>66</td>
</tr>
<tr>
<td>Nakayasu et al.</td>
<td>2011</td>
<td>RTX</td>
<td>0.35 (0.24, 0.49)</td>
<td>66</td>
</tr>
<tr>
<td>Blumberg et al. a)</td>
<td>1996</td>
<td>mixed cohort</td>
<td>0.50 (0.38, 0.62)</td>
<td>68</td>
</tr>
<tr>
<td>Wilcock et al. a)</td>
<td>2006</td>
<td>mixed cohort</td>
<td>0.44 (0.20, 0.70)</td>
<td>16</td>
</tr>
<tr>
<td>Wilcock et al. b)</td>
<td>2006</td>
<td>mixed cohort</td>
<td>0.67 (0.33, 0.88)</td>
<td>15</td>
</tr>
</tbody>
</table>
by Rodriguez-Romo et al. reported a decrease of antibodies already 28 days after vaccination after adequate levels were initially reached after the third dose of vaccine. Reduction of immunosuppression and booster doses recovered adequate antibody levels (Figure 2, category F). In both trials passive immunization may have led to an overestimation of the vaccine response. The summary response rate estimate seen in these 9 SOT recipients was 89% (95% CI: 52%–100%) (Figure 2, category F).

Long-term Response of SOT Recipients

Only few studies assessed a long-term response after ≥12 months, these were Enke et al. and Pedrazzi et al. for the tetanus trials, Huzly et al. and Pedrazzi et al. for the diphtheria, Günther et al. for hepatitis A vaccination and rabies with the caveats of passive immunization and polio long-time responses were decreasing (polio not included in the figure because absolute number of SOT recipients in the long-term cohort not assessable). A strong decline in antibodies after vaccination was also seen for hepatitis A vaccine with a decline 97.4% to 59.3% and 71.8% to 26.1%. Overall, based on this limited number of studies that assessed both short- and long-term response to vaccinations, the response for diphtheria had a 17% (95% CI: 7%–27%) and the one for hepatitis A 41% (95% CI: 26%–57%) decline over time in SOT recipients (Figure 9).

Discussion

To the best of our knowledge, this is the first systematic review of the literature on vaccination response of currently licensed vaccines in SOT recipients.

The most important finding is that most clinical trials conducted and published over more than 30 years have all been small and highly heterogeneous regarding trial design, patient cohorts selected, patient inclusion criteria, dosing and vaccination schemes, follow up periods and outcomes assessed. The evidence base for vaccination recommendations for SOT recipients thus remains poor.

Our review had two main strengths: The systematic strategy and broad search terms used to identify studies in a wide range of databases and the rigorous methods used to extract and appraise the data. The main limitation of this review was the need to rely on studies that were largely observational. The potential for confounding and bias should therefore be considered when interpreting the results and the observed level of heterogeneity of the results.
The second most important finding is that the individual vaccines investigated have been studied predominately only in one group of SOT recipients, i.e. tetanus, diphtheria and polio in RTX recipients, hepatitis A exclusively in adult LTX recipients and mumps, measles and rubella in paediatric LTX recipients. There is a clear need to investigate all recommended vaccines across all SOT types. There is increasing concern about high individual and SOT-dependant variation in the response to immunosuppressive drugs in both paediatric and adult SOT recipients [83,84].

Most trials in SOT recipients included in this review have evaluated influenza vaccines. Variability of the response was very high and ranged from 0–100% in SOT recipients with corresponding high values of I-squared (all larger than 92%). Among other reasons (such as studies conducted over more than 30 years) the varying seasonal composition of influenza vaccines may play a role and makes comparisons between trials difficult. When comparing response rates of SOT recipients with controls, several studies showed a clear trend to a less pronounced response in SOT recipients with overall a 10% to 16% lower response rate in SOT recipients. The difference in response to control patients was in renal and lung transplant recipients somewhat less pronounced than in the other SOT groups. In some studies, however, the response rate in SOT recipients was even higher than in controls, which might reflect the play of chance or the fact that in some of these studies different vaccination schemes were used in the two groups (i.e. double dose for SOT recipients and single dose for controls) or highly differing pre-transplant antibody levels (higher in SOT recipients than in controls). Almost all trials, however, observed a measurable vaccine response at least in a subset of SOT recipients after single dose vaccination with a trend to lower response rates in SOT recipients compared to healthy controls in most of the trials, which is encouraging and is in accordance with findings from other authors [85–87]. In contrast to other vaccinations, influenza vaccination is recommended annually to protect against the predicted seasonal strains; rapid decline of antibodies is, therefore, of marginal relevance. Given the susceptibility, morbidity and mortality associated with influenza infections in SOT recipients and the positive response found in most influenza vaccine trials, recommending annual influenza vaccination is encouraged by our review of published clinical trials. The benefit for accelerated vaccination schemes or multi dose vaccination to increase protection cannot be decided on the basis of available data.

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Good evidence and encouraging results were found for vaccinating SOT recipients against tetanus, diphtheria and polio. Vaccination with tetanus toxoid in the post-transplant period elicits a high rate of responders in SOT recipients with conventional immunosuppression with no significant difference to healthy controls (p = 0.96 on only two studies) while immunosuppression with anti-CD20 monoclonal antibody showed a
decreased response rate compared to conventional immunosuppressive medication ($p = 0.043$ in meta-regression). All studies with diphtheria vaccination in the post-transplant phase show comparable high response rates ($I^2 = 0\%$). From the data reviewed serological response to tetanus appears to be longer lasting than to diphtheria vaccination. Long-term response for tetanus showed persistence of antibodies without relevant decrease while the response for diphtheria had a 17\% (95\% CI: 7\%–27\%) decline over time in SOT recipients.

Response to polio vaccination also seems to be elicitable in SOT recipients, even though only one trial has investigated this vaccine. However, as polio eradication suffers from backlashes and international travel of SOT recipients is increasing, polio vaccination in SOT recipients is important and deserves further exploration.

Vaccination trials for viral hepatitis A and B have largely been conducted in LTX recipients and results can only be extrapolated to other SOT types with great care. Results for HAV vaccination show a high degree of heterogeneity ($I^2 = 97.7\%$), while one study shows high response rates for both RTX and LTX, others did not confirm this finding. Response rate to HBV after transplantation in adult SOT recipients is poor while in paediatric SOT recipients a 58\% (95\% CI: 37\%–80\%) higher response rate was seen ($p = 0.001$ from meta-regression). The results of primary vaccination after SOT are disappointing as early response rates were low in almost all trials and long-term responses have not been assessed on a large scale. In one study, however, long-term response was assessed and antibodies for HAV were declining rapidly. The response for hepatitis A had a 41\% (95\% CI: 26\%–57\%) decline over time in SOT recipients.

In the light of this finding, the importance of hepatitis A and B vaccination prior to transplantation should be markedly stressed in pre-transplant assessment and counselling. The immunogenicity of both vaccines needs to be extended beyond LTX and should be evaluated in recipients of organs other than liver.

Vaccination against bacterial pathogens is of great importance for immunosuppressed recipients. Response rate in all Streptococcus pneumoniae studies was above 50\% with a summary estimate of 83\% (95\% CI: 83\%–93\%) with substantial heterogeneity ($I^2 = 81\%$), for Haemophilus influenzae vaccines (Hib) a response rate above 50\% in SOT recipients in both studies was observed as well as for Neisseria meningitides (100\%).

Assessment of the response to pneumococcal vaccines is difficult due to the large numbers of serotypes included in the vaccines (conjugate vaccine with 7 serotypes and polysaccharide vaccine with 23 serotypes) and the unclear impact of the seroresponse measured on protection. The response rate assessed here might be overestimated as we accepted the serological response to a single antigen as positive response. However, even in healthy children and adults, vaccine-, serotype-, and population-specific differences
in immune response is not readily understood [88,89]. Most guidelines, nevertheless, recommend pneumococcal vaccines for SOT recipients. From current data it cannot be assessed if conjugate pneumococcal vaccines are superior to polysaccharide vaccines in SOT recipients.

Vaccines for protection of travel-related infections in SOT recipients have, with very few exceptions, not been studied so far. Due to increasing quality of life, SOT recipient are willing to travel and a thorough assessment of their vaccination status is therefore necessary [90,91]. Also, it is important to note that some of these infections are highly endemic or epidemic in countries where SOTs are now also regularly performed. Rabies is an example. We could identify only a single and very small trial on rabies post-exposure prophylaxis. The summary response rate estimate seen in these nine SOT recipients was 89% (95% CI: 52%–100%). These results are encouraging for rabies vaccination in SOP recipients. From a global point of view research in this area is warranted.

Vaccination of SOT recipients with live-attenuated viral vaccines remains controversial and is clinical studies are currently limited to paediatric SOT recipients [92–94]. Generally, live vaccines are contraindicated in immunocompromised recipients as there is a risk of vaccine-virus replication. As all other trials identified in our review, the trials investigating live vaccines are also underpowered to assess severe adverse events (SAEs) with appropriate accuracy. For live-attenuated varicella vaccination acceptable response rates were observed in all studies with an overall estimate of 73% (95% CI: 64%–83%) with little heterogeneity (I-squared = 0%) in SOT recipients after post-transplantation vaccination are seen. For mumps, measles and rubella positive response rates were above 70% in all but one study conducted in 1993, resulting in a summary estimate of 85% (95% CI: 72%–99%) with substantial heterogeneity (I-squared = 76%). Omitting the 1993 study reduced heterogeneity substantially (I-squared = 36%). In terms of vaccination response, the trials presented here show encouraging results at least for paediatric recipients. The trials so far performed were very small, however, and do not allow to assess the risk-benefit ratio of vaccination vs. infections for e.g. measles or varicella. The underpowerment is a problem to accurately assess vaccine-related SAEs in SOT recipients in all trials conducted so far. On theoretical grounds the risk of SAE is expected to be less in inactivated compared to live-attenuated vaccines. On the basis of currently available evidence application of live vaccines should remain limited to carefully monitored trials until more data on safety are available. Instead, indirect protection of SOT recipients by vaccination of household contacts is stressed by all authors.

Vaccination aims for long-term protection after initial immunization. To which extent this can be achieved in SOT recipients is unclear. Only few studies assessed a long-term response after ≥12 months. Long-term response for tetanus showed persistence of antibodies without relevant decrease while response for diphtheria had a 17% (95% CI: 7%–27%) and the one for...
Vaccination after Solid Organ Transplantation

hepatitis A 41% (95% CI: 26%–57%) decline over time in SOT recipients. Based on this limited number of studies that assessed both short- and long-term response to vaccinations no recommendation on adaptation of general recommendations for booster intervals for SOT recipients can be given.

Limitations of our review are that, despite the use of systematic search strategies, some trials may have been missed, particularly since the search was limited to trials published in English. We did not assess the quality of the trials. All trials included in this review were, however, published in peer-reviewed journals. Only publications in which essential key data were missing were excluded. Since we did not restrict our search to a specific publication period, older trials using out-dated immunosuppressive regimens, which are no longer relevant, may have been included. We are aware that the type of immunosuppressive treatment impacts on the vaccine response. Stratification by type of immunosuppressive treatment would have, however, further fragmented the presentation of available data with the result of even smaller numbers per stratum. Equally, we did not exclude trials on the basis of the time period between SOT and vaccination despite the fact that the first 6 months after transplantation is regarded as the period during which immunosuppression is highest.

Additional potential sources of heterogeneity in positive response to vaccination were substantial loss to follow-up and often unknown and possibly varying levels of pre-transplant response to vaccination were substantial loss to follow-up and highest.

we included all trials with relevant endpoints in well-defined SOT recipient cohorts, as well as to increase the awareness of clinicians for timely pre-transplant vaccination.

Acknowledgments

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Author Contributions

Conceived and designed the experiments: IE KDR MZ TJ. Performed the experiments: IE TJ. Analyzed the data: IE KDR MZ TJ. Contributed reagents/materials/analysis tools: IE KDR MZ TJ. Wrote the paper: IE KDR MZ TJ.

References


