Background document

Recommendations for immunization of solid organ transplant (SOT) candidates and recipients

February 2014
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Recommendations for immunization of solid organ transplant (SOT) candidates and recipients

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Federal Advisory Commission on Immunisation

Recommendations endorsed by:
The Swiss Society for Infectious Diseases (www.sginf.ch), the Swiss Transplantation Society (www.swisstransplantationsociety.com) and Swisstransplant (www.swisstransplant.org).
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1. Introduction

Solid organ transplant (SOT) recipients are at increased risk for infectious complications due to their chronic disease and to the iatrogenic immunosuppressive therapy required to prevent rejection of the allograft [1]. With respect to vaccine-preventable diseases (VPD) this risk includes:

- A higher attack rate and higher risks for severe and complicated illness, as documented e.g. for varicella [2, 3], measles [4, 5], influenza [6] and invasive pneumococcal disease [7, 8];
- Higher risks of not having been optimally immunized, delays of routine vaccinations being frequently observed in patients with chronic organ diseases even before they become SOT candidates [9–11];
- Limited efficacy and duration of vaccine-induced protection in patients with chronic organ failure [12–14] and due to post-transplant immunosuppressive treatments [15, 16], depending on both the type of organ transplant and the immunosuppressive regimen [17, 18] and affecting the induction of primary responses more than the boosting of pre-existing immunity [19].

Two main periods are characterized with respect to the relative risks of VPD and vaccination recommendations: the pre- and the post-transplant period. During each of these periods, specific recommendations prevail:

- For the evaluation and the documentation of the immunization status
- For the immunization of the patient and his household

These recommendations provide information on which vaccinations are indicated, on how to review and complete the vaccination status of the potential SOT candidate before transplantation, and on how to best evaluate the need for and the administration of catch-up and booster vaccinations in SOT recipients. For inactivated vaccines in SOT recipients, when specific data and recommendations are not available, the recommendations of the Swiss Immunization Plan (SIP) should be followed [20].

Sources of information: These guidelines are based on recent systematic and expert reviews and guidelines published in North America and Europe [18, 21–27]. Wherever possible and relevant, original studies have also been cited.

Overall, there is only few data for evidence of protection in healthy individuals. These recommendations are made on the available specific data, the administration of catch-up and booster vaccinations may have to be used [23, 24], if SIP is expected in the near future. This may also apply for patients who develop acute organ failure resulting in a need for emergency SOT, although time may be short to achieve full immunizations. In these patients, documentation of antibody responses to vaccines and careful prioritization of immunizations may be necessary.

2. Prevention of vaccine-preventable diseases in the pre-transplant period

Transplant candidates frequently suffer from severe underlying chronic disease with a predictable clinical course and may not be able to tolerate the increased risk for some VPD due to organ insufficiency even at the pre-transplant stage (e.g. hepatitis A in chronic liver disease [28], invasive pneumococcal disease in nephrotic patients [29]), these patients are often vaccinated with delay, incompletely or not at all [9–11]. Thus, updating vaccination to schedule and rapid catch-up have the highest priority before transplantation (basic and complementary vaccinations and specific at risk vaccinations). In order to achieve this aim once a chronic disease process has been diagnosed, it is necessary to define which immunizations have been completed, which are lacking or incomplete and which catch-up schedule is needed before transplantation to achieve optimal protection against VPD. In many cases an accelerated schedule may have to be used [23, 24], if SOT is expected in the near future. This evaluation and documentation of antibody responses to vaccines and careful prioritization of immunizations may be necessary.

2.1 Evaluation of vaccine-induced immunity in the pre-transplant period

Evaluation and documentation of the immunization status and the estimate of protection against VPD is of paramount importance as the incidence and the risk for severe or complicated VPD increases with progressing organ disease eventually requiring SOT and persists thereafter. This evaluation and documentation is the basis and a prerequisite to define which vaccinations are to be completed, whenever possible before SOT, in order to achieve best possible protection of the SOT candidate and recipient. It relies on the documentation of immunizations received (immunization records) and on vaccine-induced immunity (serological analyses). The recommended approach is indicated in Table 1.

2.1.1 Vaccinations records:

Once a patient is identified as having an acute or chronic disease likely to lead to SOT, it is necessary to periodically review and update documentation of immunizations (preferably including an electronic documentation which may be shared between carers, as for example on www.meine­impfungen.ch). This documentation must be available and reviewed at first contact in the transplantation centre and should be considered compulsory for listing. Note that pre-transplant documentation of completed immunizations by a healthcare professional is the strongest indicator for protection against VPD at the time of transplantation and indispensable for the interpretation of specific vaccine antibody titres. This documentation should include a documen-
Serological evaluation to document baseline and post-vaccination immunity and antibodies (Table 2) and should be determined to define immunity from vaccines/infections that confer sustained protection or lack a correlate for protection. Specific antibody levels should be determined again after immunization to document vaccine-induced immunity. Specific antibody levels against other VPD such as pertussis, mumps, HPV, meningococcal infection or influenza have either not been characterized, are not established, not available, not required to demonstrate protection or lack a correlate for protection.

The correlation of antibody levels with protection is best when the level is measured 1–3 months after completion of a primary immunization series or a booster dose. Immunity from vaccines/infections that confer sustained protection (e.g., measles, VZV) may be checked at all times. Based on data from healthy persons, correlates of protection have been established for tetanus, _Haemophilus influenzae_ type b, hepatitis A, Measles, mumps, rubella and varicella antibodies (Table 2) and should be determined to define whether there is immunity (after disease or vaccination) against particular VPD.

**2.1.2 Immunity against VPD (serology):**

Documentation of immunity against all VPD (Table 2) should be achieved before transplantation. Because it may not be possible to assume protective immune responses even from a complete vaccination history as in healthy persons, the documentation of the vaccination status in SOT recipients as well as in SOT candidates with end-stage organ disease should be completed by the determination of specific antibody titres. Determination of antibody levels as a surrogate marker for protection may be helpful when:

- it is unclear whether there is immunity (after disease or by immunization) against particular VPD
- the need for a booster immunization (e.g., tetanus, hepatitis B) must be assessed
- the response after completed primary or a booster immunization needs to be evaluated
- it is desirable to assess the likely (long term) protection.

The correlation of antibody levels with protection is best when the level is measured 1–3 months after completion of a primary immunization series or a booster dose. Immunity from vaccines/infections that confer sustained protection (e.g., measles, VZV) may be checked at all times. Based on data from healthy persons, correlates of protection have been established for tetanus, _Haemophilus influenzae_ type b, hepatitis B, measles, rubella and varicella antibodies (Table 2) and should be determined to define which vaccinations are still needed. Antibodies to hepatitis A and yellow fever also indicate immunity. Based on these results a catch-up schedule can be designed, including required booster doses.

In patients with end-stage organ disease, antibody levels should be determined again after immunization to document vaccine-induced immunity. Specific antibody levels against other VPD such as pertussis, mumps, HPV, meningococcal infection or influenza have either not been characterized, are not established, not available, not required to demonstrate protection or lack a correlate for protection.

**2.2 Immunizations in the pre-transplant period**

Completion of basic and complementary immunizations for patients with a chronic organ disease likely to result in SOT is vital to ensure optimal protection against VPD. Every effort should thus be made to ensure that transplant candidates, including their close contacts, are completely vaccinated as early as possible and in any case prior to transplantation [21–26].

The need for individual catch-up vaccinations pre-transplant is the result of the evaluation of the vaccination record and of the determination of specific antibody levels. Evaluation of the immunization records should lead to:

- catch-up basic vaccinations, including those against tetanus, diphtheria, pertussis, polio (IPV), measles, mumps, rubella, as well as for children <5 years of age also conjugated vaccines against _Haemophilus influenzae_ type b, and against pneumococcal disease, and children <5 years and adolescents 11–19 years of age against meningococcus serogroup C [20].
### Table 2
Correlate of immunity to be checked, reached and documented

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Indication for determination of specific antibody titres</th>
<th>Specific antibody (IgG) and unit</th>
<th>Interpretation of serological analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>During end-stage disease</td>
<td>After catch-up immunization</td>
<td>Post transplant</td>
</tr>
<tr>
<td></td>
<td>At pre-transplant listing</td>
<td>(pre- or post-transplant)</td>
<td>(pre- or post-transplant)</td>
</tr>
<tr>
<td>Tetanus</td>
<td>Yes, if history unclear (*)</td>
<td>If unknown serology</td>
<td>Yes</td>
</tr>
<tr>
<td>Haemophilus influenzae type b</td>
<td>Yes (children &lt; 5 years</td>
<td>Yes, (If unknown serology in children &lt; 5 years)</td>
<td>Yes (children &lt; 5 years)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Yes (#, &amp;), If unknown serology</td>
<td></td>
<td>Every 12 months</td>
</tr>
<tr>
<td>Measles</td>
<td>Yes, if unknown serology</td>
<td>Yes</td>
<td>At 12 months</td>
</tr>
<tr>
<td>Rubella</td>
<td>Yes, if unknown serology</td>
<td>Yes</td>
<td>Not if immune before SOT</td>
</tr>
<tr>
<td>Varicella</td>
<td>Yes, if unknown serology</td>
<td>Yes</td>
<td>At 12 months</td>
</tr>
</tbody>
</table>

** If history unclear, check antibody titre 4 weeks after a booster dose to define whether further doses are needed.

# Check anti-HBs IgG titre if last dose given < 5 years ago, or 4–12 weeks after completion of primary series or a booster dose;

& Include HBsAg and anti-HBc to exclude current/past infection.

¥ In immunosuppressed SOT patients, the unknown contribution of immune memory requires regular booster doses to maintain anti-HBs titers ≥ 10 IU/l at all time in patients at risk of exposure.

* Measles and VZV IgG, by commercially used tests; if positive = immune, if negative or doubtful: send serum for analysis by a more sensitive test [30] to the Laboratoire de Vaccinologie des Hôpitaux Universitaires de Genève.

** Loss of pre-existing immunity to measles / VZV may occur in SOT patients.

- identify and immunize patients not yet immune against varicella and hepatitis B (importance of ascertaining infection status) and trigger their immunization.
- Identify females > 9 years of age not yet immunised against HPV. Vaccination of boys against HPV may be considered given the enhanced risks of cancer in immunosuppressed patients.
- Administer or catchup vaccines recommended to high-risk patients (including vaccines against influenza, pneumococcal disease, hepatitis A, as well as varicella and hepatitis B (see above) and consider particular exposure pre- and post-transplant (TBE, rabies, yellow fever etc.).

Any missing vaccinations identified before transplantation should be administered as soon as possible, as indicated in Table 3. Table 4 shows the recommended accelerated schedule for vaccination of SOT candidates based on international recommendations and the SIP [20, 23, 24]. This schedule gives the minimal age for each particular vaccine and the scheme with the shortest possible immunization series.

Live vaccines (MMR, VZV, YF) should no longer be administered after the patient is included on an emergency transplantation list and SOT is considered as likely within 4 weeks.

Specific antibody levels have to be checked after specific vaccination, as described above in Table 2. If protective levels are not reached, additional immunizations and serological controls are recommended. Additional information on immunizations during the pre-transplant period is included in section 5.

### 3. Prevention of vaccine-preventable diseases in the post-transplant period

Impaired immune response under continued immunosuppression in SOT recipients is associated with an increased incidence and risk for more severe and complicated VPD through:

- Waning (and/or delayed and partial recovery) of pre-transplant immunity [32].
3.1 Evaluation of vaccine-induced immunity in SOT recipients
Evaluation and documentation of the immunization status and the estimate of protection against VPD is of paramount importance as the incidence and the risk for severe or complicated VPD increases with progressing organ disease eventually requiring SOT, and persists thereafter. This evaluation and documentation is the basis and a prerequisite to define which vaccinations are to be completed to achieve the best possible protection of the SOT recipient. The approach to evaluation of immunization status in post-transplant patients is outlined in Table 5. Please refer to Table 2 for correlates of immunity to be reached and documented.

3.2 Immunizations of SOT recipients
Immunization post-transplant is necessarily limited by immunosuppression, and live vaccine in general must not be used (varicella see below). In addition, vaccine responses under transplant-associated immunosuppression are impaired to a greater extent than during the chronic disease pre-transplant stage. Nevertheless, inactivated vaccines provide some protection [18] and these should be used whenever necessary despite their limitations.

The following principles have to be considered:

- **Exposure to VPD through non-immune close contacts** [23].

3.1 Evaluation of vaccine-induced immunity in SOT recipients
Evaluation and documentation of the immunization status and the estimate of protection against VPD is of paramount importance as the incidence and the risk for severe or complicated VPD increases with progressing organ disease eventually requiring SOT, and persists thereafter. This evaluation and documentation is the basis and a prerequisite to define which vaccinations are to be completed to achieve the best possible protection of the SOT recipient. The approach to evaluation of immunization status in post-transplant patients is outlined in Table 5. Please refer to Table 2 for correlates of immunity to be reached and documented.

### Table 3
Completion of immunizations in the pre-transplant period

<table>
<thead>
<tr>
<th>Vaccine immunogenicity</th>
<th>Basic and complementary vaccines</th>
<th>Vaccines for high risks patients</th>
<th>Documentation of immunizations</th>
</tr>
</thead>
</table>
| **Chronic disease state** | Normal or already reduced (but better than later!)
To update according to SIP [37] and to serological analyses. Use accelerated immunization schedule if needed. + No live vaccine if included on emergency transplantationist. | Yearly seasonal influenza; HAV immunization if liver disease (*). | Documentation of immunization status and of serologies (+/-) in immunization record. |
| **Progression to end-stage organ disease** | Normal or already reduced (but better than later!)
To update according to SIP and to serological analyses. Use accelerated immunization if needed. | Yearly seasonal influenza; HAV immunization if liver disease (*). | Documentation of immunization status and of serologies (+/-) in immunization record. |
| **SOT candidates** | Normal or already reduced (but better than later!)
To update according to SIP and to serological analyses.
+ Use accelerated immunization schedule if needed.
+ No live vaccine if included on emergency transplantationist.
+ Consideration should be given to yellow fever immunization which will remain contraindicated after SOT. | Yearly seasonal influenza; HAV immunization if liver disease (*). + PCV13 + MenACWY if splenic dysfunction | Documentation of immunization status in immunization record and in the referral letter to the transplant centre. |
| **Household contacts** | Normal | To update according to SIP [37] and to serological analyses.
+ Consideration should be given to yellow fever immunization which will remain contraindicated after SOT. | Yearly seasonal influenza immunization. | Documentation of immunization status in immunization record and in the referral letter to the transplant centre. |

(*), Consider exposition / travel vaccines as TBE (FSME), rabies, Hepatitis A, Yellow Fever, meningococcal infections, etc. according to exposition risks before and after transplant. Special consideration should be given to yellow fever immunization which will remain contraindicated after SOT.
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Table 4
Recommended accelerated vaccination schedule in the pre-transplant period

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Minimum age</th>
<th># doses</th>
<th>Schedule (minimal interval in months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTP&lt;sub&gt;a&lt;/sub&gt;, IPV</td>
<td>6 weeks (&gt;7 years dTP)</td>
<td>first dose &lt; age 1 year: 4 doses ≥ 1 year: 3 doses</td>
<td>0, 1, 2, + 1x ≥ 12 months 1&lt;sup&gt;a&lt;/sup&gt; 0, 1, 6&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>dT(p,) booster</td>
<td>8 years</td>
<td>1 dose every 10 years</td>
<td></td>
</tr>
<tr>
<td>Hib</td>
<td>6 weeks</td>
<td>first dose &lt; 1 year: 4 doses 12–59 months: 2 doses</td>
<td>0, 1, 2, + 1x ≥ 12 months 1&lt;sup&gt;a&lt;/sup&gt; 0, 2</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Birth</td>
<td>3 doses (hexavalent vaccines or rapid schedule: 4 doses; 11–15 years: 2 adult doses)</td>
<td>0, 1, 4 (1–3 primary doses + booster after ≥ 4 months)</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>6 months (off label &lt; 1 years)</td>
<td>2 doses</td>
<td>0, 4</td>
</tr>
<tr>
<td>PCV13</td>
<td>6 weeks (off label &gt; 5 years)</td>
<td>first dose &lt; 1 year: 3–4 doses 1 year: 2 doses &gt; 1 year: 1 dose</td>
<td>0, 1, 2 + 1x ≥ 12 months 1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Influenza</td>
<td>6 months</td>
<td>children &lt; 9 years: 2 doses in first season</td>
<td>if 2 doses: 4 weeks interval.</td>
</tr>
<tr>
<td>MMR</td>
<td>6 months</td>
<td>2 doses</td>
<td>0,1&lt;sup&gt;a,b&lt;/sup&gt; 4</td>
</tr>
<tr>
<td>Varicella</td>
<td>6 months</td>
<td>2 doses</td>
<td>0,1&lt;sup&gt;a,b&lt;/sup&gt; 4</td>
</tr>
<tr>
<td>HPV (women)</td>
<td>9 years</td>
<td>2 doses if first dose &lt; 15 years; 3 doses if first dose ≥ 15 years</td>
<td>0, (1), 4</td>
</tr>
<tr>
<td>MenACWY conjugate&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 year (off label &lt; 11 years)</td>
<td>2 doses (+ booster to be considered every 5 years)</td>
<td>0, 2</td>
</tr>
</tbody>
</table>

1<sup>a</sup> 3 doses in the first year of life: 4. dose a) > 6 months after dose 3 and b) after 12 months of age.
2<sup>a</sup> further DTP, IPV at age 4 (–7) years, see SIP
3<sup>a</sup> If first dose < 12 months of age, give 2nd dose after 12 months of age or include a 3rd dose after 12 months of age.
4<sup>a</sup> prefer MenACWY conjugate vaccine to polysaccharide vaccine [31]

competence under intense iatrogenic immunosuppression during the first months after SOT. Thus, at present it is recommended to wait for 6 to 12 months after SOT before revaccination (with inactivated vaccines) [23]. A notable exception is immunization against seasonal influenza, which may be recommended at all times after transplant to hopefully elicit at least partial immunity.

- Waning immunity has been recognized in previously immunized SOT recipients with positive antibody titres before and lower/undetectable titres after transplantation [24]. Breakthrough disease and liver rejection has also been documented in a previously immunized liver transplant recipient [47]. Factors such as the administration of a single instead of two vaccine doses, the type of immunosuppression (use of mycophenolate mofetil) or the failure to maintain an immunologic memory all may contribute to the observed waning of immunity [17, 24, 32, 48–51]. Despite waning immunity, immunization before transplant generates immune memory which can often be successfully boosted post-transplant.

Thus, pre- and post-transplant immunizations are important and likely to provide the best possible protection against VPD.

Table 5 indicates how to evaluate, elicit or update vaccine-induced protection in SOT recipients. Note that it is essential for every period:

1. to review immunization records to identify missing immunizations.
2. to document immunization status in the immunization record.

When vaccinations are administered post-transplant (Table 5), a normal immune response cannot be assumed. As opposed to routine immunizations in otherwise healthy individuals, it is therefore recommended to assess specific vaccine antibody responses to as surrogate markers for protection (Table 2) and to define if additional doses should be recommended.

4. Cocooning: Immunization of close contacts of SOT recipients

Close contact persons of SOT patients are the family members (persons living in the same household) as well as the health care personnel taking care of SOT recipients. The immunization status of all close contacts should be reviewed along the schedule suggested in the SIP and missing vaccinations should be completed as soon as possible. Due to the high risk of the following VPD for SOT recipients and the potentially incomplete protection of SOT recipients, the immunity of close contacts against these VPD should be checked and/or induced by vaccination. Close contacts should be evaluated for immunity by history (e.g., varicella) and if immunity is unknown or the person is not immune, the following vaccinations are recommended (evidence II-2) [23]:


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Table 5
Evaluation and completion of immunizations in SOT recipients

<table>
<thead>
<tr>
<th>Evaluation (see also pre-transplant evaluation)</th>
<th>Immune competence and vaccine responses</th>
<th>Basic and complementary vaccines</th>
<th>Vaccines for high risks patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months after SOT</td>
<td>Immunization record: review and identify missing vaccinations, including 1x PCV13 before SOT. Serological analyses: none</td>
<td>Markedly reduced</td>
<td>Generally not recommended</td>
</tr>
<tr>
<td>12 months after SOT</td>
<td>Immunization record: review</td>
<td>Reduced (proportional to immunosuppression regimen)</td>
<td>To update according to serological analyses.</td>
</tr>
<tr>
<td>Follow-up post-transplant period</td>
<td>Immunization record: review. Serological analyses: Tetanus, (Hib), HBV, measles, VZV</td>
<td>Catchup + update of inactivated vaccines (varicella see below) according to SIP [37] and serological analyses.</td>
<td>Yearly seasonal influenza immunization</td>
</tr>
<tr>
<td>Household contacts</td>
<td>Immunization record: review</td>
<td>Normal</td>
<td>To update according to SIP [37] including VZV vaccines already during childhood</td>
</tr>
</tbody>
</table>

Table 6
Immunizations for cocooning

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Indication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>All</td>
<td>Yearly</td>
</tr>
<tr>
<td>Varicella</td>
<td>If negative history: serology* if negative serology: immunize</td>
<td>2 doses (interval &gt; 4 weeks)</td>
</tr>
<tr>
<td>MMR</td>
<td>If 2 doses are not documented: immunize</td>
<td>2 doses (interval &gt; 4 weeks)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>All close contacts if not yet immunized</td>
<td>3 doses (0,1,6 months)</td>
</tr>
</tbody>
</table>
* not needed in young children with negative history

As a general principle, non-live vaccines should be preferred to live vaccines for close contacts of immunosuppressed patients if available (for example inactivated IPV and influenza vaccines instead of live oral polio or nasal influenza vaccines). However, there is no identified risk of transmission of MMR and minimal risk of transmission of VZV vaccines from close contacts [43]. The protection of the SOT recipient from transmission of wild type virus thus largely outweighs the only theoretical risks associated with the use of live attenuated vaccines for close contacts.

5. Recommendations for individual immunizations in the pre- or post-transplant periods

This section provides the baseline evidence on which the current recommendations are based.

5.1 Basic and complementary immunizations

**dTPa, (IPV)**

There are no data on the incidence or severity of tetanus, diphtheria, or pertussis in transplant recipients. Vaccination with DTPa/dT is safe and immunogenic in paediatric populations with end-stage renal and/or end-stage liver disease and immunogenic in paediatric SOT recipients [18, 52, 53]. Antibody responses are reduced and antibodies are lost at a more rapid rate in SOT recipients compared with healthy controls [18, 52, 54]. In accordance with the SIP, DT/dTIP/a and IPV should be administered to SOT candidates as...
detailed in the general schedule. DT/dTP/v/ as inactivated vaccine can be given to post-transplant patients [21–23]. Although limited, there is some evidence that this inactivated vaccine is efficacious in SOT recipients [18, 19].

Haemophilus influenzae type b (Hib) Immunization against Haemophilus influenzae type b should be considered according to recommendations for the vaccination of less than 5-year-old children in the SIP. It is not recommended in children older than 5 years and in adult SOT candidates and recipients. In children with end-stage organ disease it is recommended that antibody titres should be checked and a booster dose given if the titre is below the threshold (Table 2). Hib immunization post-transplant is expected to be less immunogenic than before. Nevertheless it is recommended in children <5 years of age requiring catch-up, as it is reported to be effective in well-functioning paediatric renal allograft recipients [55].

MMR In the pre-transplant period, two doses of MMR vaccine at least one month apart are recommended. The first MMR dose is usually recommended at the age of 12 months, but can be performed at the age of 6 months if required [20]. It is crucial to give two doses up to one month before transplantation, as this vaccine is contraindicated thereafter. If earlier vaccination is not documented, the adult transplant candidate (born after 1963) should be considered non-immune and receive two doses of MMR before transplanta- tion. In cases of doubt, serological evaluation may help confirm immunity (Table 2). Currently, there is insufficient data to generate evidence-based guidelines for the use of MMR in transplant recipients under immunosuppression. Preliminary data on efficacy and safety suggest that the use of MMR in paediatric SOT recipients could be a reasonable strategy [42, 56, 57] and one study is currently ongoing in Switzerland with liver transplant children (Posfay-Barbe, K, personal communication). Indeed, additional evidence is needed before this can be widely recommended. Meanwhile the importance of pre-transplant immunization of SOT candidates and close contacts cannot be overemphasized.

Hepatitis B SOT recipients may have more severe and more rapidly progressive hepatitis B (HBV) infection and may also reactivate latent disease while under immunosuppression [28, 58, 59]. HBV vaccination may provide protection against donor derived infection, particularly important in settings where HBV is endemic [60–62]. HBV vaccination is recommended for patients with end-stage renal and liver disease [20, 23]. Where unknown, HBV serology including the assessment of evidence of past or active infection (presence of HBs-antigen, anti-HBs and anti-HBc) must be assessed before any further steps including immunization. If there is evidence of past or active HBV infection, further evaluation (HBV-DNA, liver biopsy; indication for antiviral treatment) of the candidate in discussion with liver and infectious diseases specialists must be undertaken. In the HBV naive SOT candidate or recipient the standard immunisation series is to be used with 3 doses (see SIP) and anti HBs serology checked 1–3 months after completion. Since response to primary HBV vaccination may be impaired in patients with cirrhotic liver or chronic renal disease, it is particularly important to start immunizations as early as possible in these patients if HBV vaccines were not administered as part of routine immunizations [63]. As for most vaccines a poorer response has been described for patients post-transplant compared with the normal population [64, 65] with some evidence of the benefits of receiving primary HBV immunisations prior to SOT with good response to boosters in this group [66]. Since there is a strong correlation between post-vaccination titres and the protective effect of HBV immunisation, monitoring of anti-HBs serology post-immunisation is recommended in SOT candidates and recipients. If 4 weeks after the primary course the anti-HBs titre is <10 IU/l, additional doses should be administered. Thereafter if the titre remains <10 IU/l, administration of combined vaccine against Hepatitis A and Hepatitis B (Twinrix®) or high dose HBV vaccine (40ug HBs-antigen) can be tried and has vari- ously been reported to be more or less successful [67–73]. Monitoring of anti-HBs titres after primary immunization series, at pre-transplant evaluation and after transplantation is recommended with subsequent application of booster doses if the titre is <10 IU/l [22, 66]. An anti-HBs titre >100 IU/l should be documented 4 weeks after boosting.

HPV Transplant recipients with anogenital HPV infection are at 20–100-fold increased risk of cervical intraepithelial neoplasia and other anogenital malignancies [74, 75]. At the present time, no published studies of immunogenicity of this vaccine in transplant recipients and candidates are yet available [76]. Since it is an inactivated vaccine, it could theoretically be safely given after transplantation. For optimal response, it is however preferable to administer HPV vac- cine to SOT candidates before transplantation to girls aged >9 years. However, HPV vaccines are very immunogenic and should be considered for any transplant patient at risk of exposure. The use of HPV vaccine may also be consid- ered in boys >9 years of age.

MenC disease Transplant recipients may be given MenC conjugate vac- cine according to the SIP (1–5 years and 11–19 years). Immunization against MenACWY is recommended to patients with splenic dysfunction or other risk factors [31] see in the section immunization for high risk subjects below.

Pneumococcal disease Immunization against invasive pneumococcal disease with 13-valent pneumococcal conjugate vaccine should be considered according to recommendations for the vaccination of less than 5-year-old children in the SIP. Immunization of groups at high risk for invasive pneumococcal disease including transplant candidates and recipients [77] see im- munization of high risk subjects below.

Immunizations for high risk subjects

Influenza Influenza infection in patients with chronic illness and SOT recipients is associated with increased morbidity and mor- tality, including severe pulmonary and extrapulmonary
complications and may lead to decompensation [36, 78–80]. Immunosuppressed patients with influenza infection have prolonged viral shedding [81, 82] and are at increased risk of allograft rejection [36, 83, 84]. In contrast, influenza immunization is not associated with a risk for development of allograft rejection after vaccination [33, 35, 36, 85, 86]. The influenza vaccine has been shown to be safe in SOT recipients, but to yield adequate antibody responses only in a part of SOT recipients [85, 87–89]. The specific immunosuppressive regimen might contribute to the size of any impairment of the response to the vaccine [45, 90–93]. Given the limited immune response to influenza vaccinations in SOT recipients, approaches to increase the immune response have been tried using intradermal application [94–96] or using, for example, MF-59 adjuvanted vaccine [97–102] with variable success.

Annual influenza vaccination is recommended for all patients with progressive chronic organ disease likely to eventually result in SOT, SOT candidates and recipients, beginning 6 months after transplantation. Earlier vaccination during the period of maximum immunosuppression during the first 6 months post-transplant has been shown to produce low antibody titres in recipients of kidney transplants [103]. To increase the immune response, SOT recipients may be given a two-dose course of influenza immunization instead of an annual single shot after individualized risk assessment, but current data do not allow for recommending an annual two dose schedule [18, 87, 104–108].

Invasive pneumococcal disease

Invasive pneumococcal infections can cause significant morbidity and mortality in SOT recipients [109]. Pneumococcal vaccination is currently recommended in patients with chronic organ disease, including e.g. cardiovascular, renal, and liver disease (see SIP) [20, 23], as well as in SOT candidates and recipients [23]. As with other vaccines, protective antibody titres are less reliably induced and known to decrease with time in patients with end-stage renal or end-stage liver disease and even more after SOT [110–112]. Thus vaccination is recommended to be given as early as indicated [77] in patients with chronic disease.

Available vaccines include the 13-valent conjugate vaccine (PCV13) and the 23-valent polysaccharide vaccine (PPSV23). Vaccination for children <1 year at risk includes PCV13 given as a four-dose series [2, 4, 6, and 12–15 months][20]. Children <5 years of age, and immunocompromised children of any age who have been previously fully immunized with the PCV7 should receive one supplemental dose of PCV13. The data on immune responses to PCV (PCV7) in paediatric SOT recipients show that despite a response to initial vaccination, those to subsequent doses are lower and more transient than in healthy controls [113].

While the immune response in adult SOT recipients and other immunocompromised persons after one dose of either PPSV23 or PCV7 were similar after priming with PCV7 and boosting with PPSV23 [114, 115], another study in children showed impressively good responses in children given 2–3 doses of PCV7 only after >1 year after transplantation [116]. The available data from SOT recipients and other immunocompromised persons, including in particular those with impaired T-cell function as in HIV infection or after stem cell transplantation show increasing evidence for better efficacy and non-inferior immunogenicity of PCV in comparison with PPSV [117–123]. Based on these findings, the short and limited effect of PPSV23, the risk for hyporesponsiveness after repeated immunization with PPSV23 and the small difference in the coverage of the additional 10 serotypes only included in PPSV23 given the current epidemiology of invasive pneumococcal disease in Switzerland, PPSV23 is not recommended instead of or in addition to PCV13 in SOT candidates and recipients. As PCV13-induced protection is also likely to be limited in time, one dose of PCV13 should be administered at listing and immunity boosted with a 2nd dose at 12 months after SOT. If a patient was not vaccinated with PCV13 before SOT, PCV13 catch-up should be given at 6 months post transplant. The booster dose at 12 months post-transplant, when immunosuppression is reduced, remains recommended regardless of the interval since the last dose.

PCV13 has been licensed by FDA and EMA (but not by Swissmedic) for immunocompromised persons with high risk for invasive pneumococcal infections and is recommended for such patients by the CDC/ACIP since 2012 [124]. Due to the lack of licensure of PCV13 use in adults by Swissmedic, this recommendation is off-label and may thus not be reimbursed by health insurances in Switzerland.

Invasive meningococcal disease

Immunization against MenACWY should be recommended to all SOT candidates and recipients with splenic dysfunction. The conjugate vaccine (Menveo®, Novartis vaccines) is more immunogenic and should be preferred to the polysaccharide vaccine (Mencevax®). Booster doses should be considered every 5 years, especially if there is an exposure to meningococci serogroup A [31].

Varicella

Varicella is known to cause severe disease especially in immunocompromised hosts [125]. Despite the availability of a life-attenuated varicella zoster virus (VZV) vaccine (Varilrix®, Varivax®) with an efficacy of 70–90% against chickenpox and >95% against severe disease in healthy hosts, VZV circulation is definitely persisting in the community, thus posing a risk for susceptible SOT recipients, children in particular.

Live-attenuated VZV immunization in end-stage renal diseases and in SOT candidates is safe and effective [51, 126, 127]. As most adult transplant candidates are already immune to varicella, the disease history however is rarely documented. VZV serology (IgG) is thus recommended for all candidates. If VZV IgG is negative (Table 2) – and for children >9 months of age without a history of chickenpox – immediate VZV vaccination (two doses one month apart) is highly recommended.

Varicella vaccination before transplantation is essential as, SOT candidates and recipients are a high-risk group, vaccine responses are better before than after SOT, and the live attenuated VZV vaccine is officially contraindicated in immunocompromised patients. However, varicella vaccination has been studied in paediatric SOT recipients and accumulating evidence shows this vaccine to be safe and immunogenic in SOT recipients. While a vaccine response (protective antibody titre and cellular immunity) was seen in >70% up to 100% of paediatric SOT recipients (kidney and liver), unwanted local and systemic effects including
vaccine-induced varicella were mild and transient [18, 30, 57, 128–130]. Breakthrough disease was reported with a cumulative incidence of 0–25%, was mostly mild, rarely requiring hospital admission or antiviral treatment and occurred only in VZV antibody-negative SOT recipients [131]. Although these studies are and will remain underpowered to assess efficacy and severe adverse events, they allow considering varicella immunization in seronegative SOT recipients with minimal immunosuppression, the expected benefits (protection from varicella in countries where viral circulation is widespread) outweighing the theoretical risks of VZV vaccination (extensive viral replication, which could be controlled by antivirals).

Varicella vaccine is thus not only a first priority in susceptible SOT candidates but also to be considered and recommended in stable VZV-seronegative SOT recipients with minimal immunosuppression if immunization before SOT did not occur and/or VZV immunity has waned.

**Herpes zoster**

Reactivation of VZV after primary infection, or herpes zoster infection, occurs with increased incidence in immunocompromised hosts, including SOT recipients [132–134]. For prevention or mitigation of herpes zoster, a live attenuated zoster vaccine was developed. This vaccine is composed of the same viral strain (Oka) as the varicella vaccine but has a distinct (i.e.14-fold) higher virus titre. This vaccine should not be used in varicella naïve persons or person previously immunized with varicella vaccine. Despite the ACIP statement [135], it is currently neither available nor recommended in Switzerland – and clearly contraindicated after transplantation [136].

**Hepatitis A**

Hepatitis A virus (HAV) can cause severe disease and fulminant hepatitis in patients with chronic viral hepatitis and in end-stage liver disease [137–140]. Vaccination against hepatitis A is thus recommended [20, 23] for patients with end-stage liver disease and may be considered in all SOT candidates at risks of exposure (travel) [28]. Antibody titres in response to hepatitis A vaccination are lower in patients with end-stage liver disease, and even more after SOT, compared to healthy subjects and may more rapidly decrease after SOT [16, 65, 141–143]. If immunization is performed after SOT, HAV responses should thus be assessed 1–3 months after the second dose and a single HAV booster be administered to non-responders [22, 23, 143].

**Other vaccinations (risk based assessment)**

Every inactivated vaccine can be safely administered to SOT candidates and recipients. The potentially risks of poorer vaccine responses has to be taken into account, in particular in immunosuppressed SOT recipients. An individual discussion is strongly recommended to define the risk of exposure and discuss the possibility of providing protection against other vaccine-preventable disease. This may include vaccinations against TBE (FSME), hepatitis A, rabies, meningococcal disease or yellow fever (only before SOT) when travel-associated exposure may be relevant.

In general, unless specifically indicated otherwise in this document, live vaccines are contraindicated after SOT.
Recommendations for immunization of solid organ transplant (SOT) candidates and recipients

Background document

Recommendations for immunization of solid organ transplant (SOT) candidates and recipients


77. Eidgenoessische Kommision fuer Impffragen (EKIF) and Bundesamt fuer Gesundheit, Editor 2011: Bern.


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