General Best Practice Guidelines for Immunization

Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP)

INTRODUCTION
Purpose and topics covered in this report...

METHODS
Method of development of: Timing and Spacing, Contraindications and Precautions, Preventing and Managing Adverse Reactions...

TIMING AND SPACING OF IMMUNOBIOLOGICS
Vaccine scheduling, supply and lapsed schedule, spacing of doses, simultaneous and nonsimultaneous administration, licensed combination
General Best Practice Guidelines = General Recommendations
General Recommendations on Immunization

- ACIP MMWR Table of Contents
  - Timing and spacing
  - Contraindications and precautions
  - Preventing and managing adverse reactions to immunization
  - Vaccine administration
  - Storage and handling
  - Altered immunocompetence
  - Special situations
  - Vaccination records
  - Vaccination programs
  - Vaccine information sources
General Recommendations on Immunization

- *Pink Book chapter*
  - Timing and spacing
  - Contraindications and precautions
Timing and Spacing Issues

- Interval between receipt of antibody-containing blood products and live vaccines

- Interval between doses of different vaccines not administered simultaneously

- Interval between subsequent doses of the same vaccine
Antibody-containing Blood Products

- Used to restore a needed component of blood or provide a passive immune response following disease exposure.

- Sometimes circumstance dictates the use of antibody-containing blood products along with a vaccine.
Antibody and Live Vaccines

General Rule

- Inactivated vaccines are generally not affected by circulating antibody to the antigen

- Live, attenuated vaccines might be affected by circulating antibody to the antigen – an effectiveness concern
## Antibody Products and Measles- and Varicella-containing Vaccines

<table>
<thead>
<tr>
<th>Product given first</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine</td>
<td>Wait 2 weeks before giving antibody</td>
</tr>
<tr>
<td>Antibody</td>
<td>Wait at least 3 months before giving vaccine</td>
</tr>
</tbody>
</table>
Appendix A24: Interval Between Antibody-containing Products and Measles- and Varicella-containing Vaccines

<table>
<thead>
<tr>
<th>Product / Indication</th>
<th>Dose, Including mg Immunoglobulin G (IgG/kg body weight)</th>
<th>Recommended Interval before measles or varicella-containing vaccine administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood transfusion</td>
<td>10 mL/kg (normal IgG/kg) IV</td>
<td>None</td>
</tr>
<tr>
<td>- Red blood cells (RBCs), washed</td>
<td>10 mL/kg (10 mg IgG/kg) IV</td>
<td>3 months</td>
</tr>
<tr>
<td>- Adult RBCs, saline added</td>
<td>10 mL/kg (0-100 mg IgG/kg) IV</td>
<td>6 months</td>
</tr>
<tr>
<td>- Whole blood (hematocrit 30%-50%)</td>
<td>10 mL/kg (100 mg IgG/kg) IV</td>
<td>3 months</td>
</tr>
<tr>
<td>- Washed plasma products</td>
<td>10 mL/kg (100 mg IgG/kg) IV</td>
<td>3 months</td>
</tr>
<tr>
<td>Botulin Immune Globulin Intravenous (Human)</td>
<td>1.5 mL/kg (25 mg/kg) IV</td>
<td>5 months</td>
</tr>
<tr>
<td>Cytomegalovirus IgV</td>
<td>150 mg/kg maximum</td>
<td>5 months</td>
</tr>
<tr>
<td>Hepatitis A Ig</td>
<td>0.32 mL/kg (3.3 mg/kg) IM</td>
<td>3 months</td>
</tr>
<tr>
<td>- Contact prophylaxis</td>
<td>0.36 mL/kg (10 mg/kg) IM</td>
<td>3 months</td>
</tr>
<tr>
<td>- International travel</td>
<td>0.36 mL/kg (10 mg/kg) IM</td>
<td>3 months</td>
</tr>
<tr>
<td>Hepatitis B Ig (Hepatitis)</td>
<td>0.36 mL/kg (10 mg/kg) IM</td>
<td>3 months</td>
</tr>
<tr>
<td>IGV</td>
<td>300-400 mg/kg IV</td>
<td>0 months</td>
</tr>
<tr>
<td>- Replacement therapy for immune deficiencies</td>
<td>400 mg/kg IV</td>
<td>0 months</td>
</tr>
<tr>
<td>- Measles Ig, contact prophylaxis (immunocompromised)</td>
<td>400 mg/kg IV</td>
<td>0 months</td>
</tr>
<tr>
<td>- Pre-exposure varicella prophylaxis</td>
<td>400 mg/kg IV</td>
<td>0 months</td>
</tr>
<tr>
<td>- Measles Ig, contact prophylaxis (standard)</td>
<td>1,000 mg/kg IV</td>
<td>10 months</td>
</tr>
<tr>
<td>Measles Ig, contact prophylaxis (immunocompromised)</td>
<td>400 mg/kg IV</td>
<td>0 months</td>
</tr>
<tr>
<td>- Monoclonal antibody to respiratory syncytial virus F protein</td>
<td>5 mg/kg (IM)</td>
<td>0 months</td>
</tr>
<tr>
<td>Rabies Ig (RIG)</td>
<td>32 IU/kg (20 mg IgG/kg) IM</td>
<td>4 months</td>
</tr>
<tr>
<td>Tetanus Ig (TIG)</td>
<td>260 units (10 mg IgG/kg) IM</td>
<td>3 months</td>
</tr>
<tr>
<td>Varicella Ig</td>
<td>125 units/10 kg (200-220 mg IgG/kg) IM, maximum 625 units</td>
<td>5 months</td>
</tr>
</tbody>
</table>

This table is not intended for determining the correct indications and dosages for using antibody-containing products. Unvaccinated persons might be fully protected against measles if the antibody content of the product is high enough. Additional doses of IgG or measles vaccine might be indicated after measles exposure. Concentrations of measles antibody in an IgG preparation can vary by manufacturer's lot. Rates of antibody clearance after receipt of an IgG preparation also may vary. Recommended intervals are extrapolated from an estimated half-life of 30 days for passively acquired antibody and an observed interference with the immune response to measles vaccine for 1 month after a dose of 20 mg IgG/kg.

1. Does not include zoster vaccine. Zoster vaccine may be given with antibody-containing blood products.
2. Assumes a serum IgG concentration of 11 mg/ml.
3. Measles vaccination is recommended for children with mild or moderate immunosuppression from human immunodeficiency virus (HIV) infection, and varicella vaccination may be considered for children with mild or moderate immunosuppression from HIV, but both are contraindicated for persons with severe immunosuppression from HIV or any other immunosuppressive disorder.
4. Contains antibody only to respiratory syncytial virus.
5. Licensed Varicella is a purified human IgG preparation made from plasma containing high levels of anti-varicella antibodies (IgG).

Adapted from Table 3, ACIP General Recommendations on Immunization

June 2014

Centers for Disease Control and Prevention
Epidemiology and Prevention of Vaccine-Preventable Diseases, 10th Edition

April 2015
## Spacing of Antibody-containing Products and MMR and Varicella Vaccines

<table>
<thead>
<tr>
<th>Product</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Washed red blood cells</td>
<td>0 months</td>
</tr>
<tr>
<td>Hepatitis A (IG)</td>
<td>3 months</td>
</tr>
<tr>
<td>Measles prophylaxis (IG)</td>
<td>6 months</td>
</tr>
<tr>
<td>(immunocompetent recipient)</td>
<td></td>
</tr>
<tr>
<td>Plasma/platelet products</td>
<td>7 months</td>
</tr>
<tr>
<td>Intravenous immune globulin (IGIV)</td>
<td>7-11 months</td>
</tr>
</tbody>
</table>
Products Containing Type-specific or Negligible Antibody

- **Palivizumab (Synagis)**
  - Contains only monoclonal RSV antibody
  - Does not interfere with live virus vaccination

- **Red blood cells (RBCs), washed**
  - Negligible antibody content
Interval Between Doses of Different Vaccines

- Simultaneous administration
- Non-simultaneous administration
Simultaneous Administration

General Rule

- All vaccines can be administered at the same visit as all other vaccines.

Exceptions:
- PCV13 and PPSV23: Give PCV13 first
- MCV4-D (Menactra only) and PCV13 in asplenic or HIV infected persons: Give PCV13 first
# Non-simultaneous Administration: Live-vaccine Effectiveness

<table>
<thead>
<tr>
<th>Combination</th>
<th>Minimum interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 live injected OR</td>
<td>4 weeks</td>
</tr>
<tr>
<td>1 live injected and 1 intranasal influenza vaccine</td>
<td></td>
</tr>
<tr>
<td>All other vaccines</td>
<td>None</td>
</tr>
</tbody>
</table>
Spacing of Live Vaccines Not Given Simultaneously

- If 2 live parenteral or intranasal vaccines are given less than 28 days apart, the vaccine given second should be repeated.

- Antibody response from first vaccine interferes with replication of second vaccine.
Intervals Between Doses

General Rule

- Increasing the interval between doses of a multidose vaccine **does not** diminish the effectiveness of the vaccine.
Extended Interval Between Doses

- Not all variations among all schedules for all vaccines have been studied

- Available studies of extended intervals have shown no significant difference in final titer

- It is not necessary to restart the series or add doses because of an extended interval between doses
Intervals Between Doses

General Rule

- **Increasing** the interval between doses of a multidose vaccine does not diminish the effectiveness of the vaccine.

- **Decreasing** the interval between doses of a multidose vaccine may interfere with antibody response and protection.
<table>
<thead>
<tr>
<th>Vaccines and doses</th>
<th>Recommended age for first dose</th>
<th>Minimum age for first dose</th>
<th>Recommended interval to next dose</th>
<th>Minimum interval to next dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV, Gardasil</td>
<td>2 months</td>
<td>12 months</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Measles, mumps, and rubella (MMR)</td>
<td>12 months</td>
<td>12 months</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>1 month</td>
<td>1 month</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Polio</td>
<td>2 months</td>
<td>12 months</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Diphtheria, tetanus, and diphtheria, tetanus, and acellular pertussis (DTaP)</td>
<td>2 months</td>
<td>6 months</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Influenza</td>
<td>12 months</td>
<td>12 months</td>
<td>6 months</td>
<td>6 months</td>
</tr>
</tbody>
</table>

Included in Pink Book Appendix A-13
<table>
<thead>
<tr>
<th>Vaccine and dose number</th>
<th>Recommended age for this dose</th>
<th>Minimum age for this dose</th>
<th>Recommended interval to next dose</th>
<th>Minimum interval to next dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria-tetanus-acellular pertussis (DTaP)-1&lt;sup&gt;5&lt;/sup&gt;</td>
<td>2 months</td>
<td>6 weeks</td>
<td>8 weeks</td>
<td>4 weeks</td>
</tr>
<tr>
<td>DTaP-2</td>
<td>4 months</td>
<td>10 weeks</td>
<td>8 weeks</td>
<td>4 weeks</td>
</tr>
<tr>
<td>DTaP-3</td>
<td>6 months</td>
<td>14 weeks</td>
<td>6-12 months</td>
<td>4 months&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>DTaP-4&lt;sup&gt;6&lt;/sup&gt;</td>
<td>15-18 months</td>
<td>12 months&lt;sup&gt;6&lt;/sup&gt;</td>
<td>3 years</td>
<td>6 months</td>
</tr>
<tr>
<td>DTaP-5</td>
<td>4-6 years</td>
<td>4 years</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Haemophilus influenzae type b (Hib)-1&lt;sup&gt;b&lt;/sup&gt;,&lt;sup&gt;7&lt;/sup&gt;</td>
<td>2 months</td>
<td>6 weeks</td>
<td>8 weeks</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Hib-2</td>
<td>4 months</td>
<td>10 weeks</td>
<td>8 weeks</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Hib-3&lt;sup&gt;8&lt;/sup&gt;</td>
<td>6 months</td>
<td>14 weeks</td>
<td>6-9 months</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Hib-4</td>
<td>12-15 months</td>
<td>12 months</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hepatitis A (HepA)-1&lt;sup&gt;5&lt;/sup&gt;</td>
<td>12-23 months</td>
<td>12 months</td>
<td>6-18 months</td>
<td>6 months</td>
</tr>
<tr>
<td>HepA-2</td>
<td>≥18 months</td>
<td>18 months</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hepatitis B (HepB)-1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Birth</td>
<td>Birth</td>
<td>4 weeks-4 months</td>
<td>4 weeks</td>
</tr>
<tr>
<td>HepB-2</td>
<td>1-2 months</td>
<td>4 weeks</td>
<td>8 weeks-17 months</td>
<td>8 weeks</td>
</tr>
<tr>
<td>HepB-3&lt;sup&gt;y&lt;/sup&gt;</td>
<td>6-18 months</td>
<td>24 weeks</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
Minimum Intervals and Ages

- Vaccine doses should not be administered at intervals less than the minimum intervals or earlier than the minimum age.
When Can Minimum Intervals Be Used?

- Catch-up for a lapsed vaccination schedule
- Impending international travel
- NOT to be used routinely
The “Grace Period”

- ACIP recommends that vaccine doses given up to four days before the minimum interval or age be counted as valid

- Should not be used for scheduling future vaccination visits

- Use for reviewing vaccination records
Use of the “Grace Period”

- To schedule a future appointment  NO!
- When evaluating a vaccination record  Yes
- Client is in the office or clinic early  Maybe
Use of the “Grace Period”

- Client is in the office or clinic
  - Client/parent is known and dependable
    - Reschedule
  - Client/parent is unknown or undependable
    - Vaccinate
Use of the “Grace Period”

- Basic principles
  - The recommended interval or age is preferred
  - The minimum interval can be used to catch up
  - The grace period is last resort
Violations of Minimum Intervals and Minimum Ages

- Grace period may conflict with some state school entry requirements

- Immunization programs and/or school entry requirements may not accept some or all doses given earlier than the minimum age or interval, particularly varicella and/or MMR vaccines

- Providers should comply with local and/or state immunization requirements
Violations of Minimum Intervals and Minimum Ages

- Minimum interval/age has been violated
  - Dose invalid

- The repeat dose should be administered at least a minimum interval from the invalid dose
Contraindications and Precautions
Vaccine Adverse Reaction

- Adverse reaction
  - Extraneous effect caused by vaccine
  - "Side effect"
Vaccine Adverse Reaction

- Adverse reaction

- Adverse event
  - Any medical event following vaccination
  - May be true adverse reaction
  - May be only coincidental
Vaccine Adverse Reactions

- Local

  - Pain, swelling, redness at site of injection
  - Common with inactivated vaccines
  - Usually mild and self-limited
Vaccine Adverse Reactions

- Local

- Systemic

  - Fever, malaise, headache

  - Nonspecific

  - May be unrelated to vaccine
Live, Attenuated Vaccines

- Must replicate to produce immunity
- Symptoms usually mild
- Occur after an incubation period (usually 3-21 days)
Vaccine Adverse Reactions

- Local

- Systemic

- Allergic
  - Due to vaccine or vaccine component
  - Rare
  - Risk minimized by screening
Contraindication

- A condition in a recipient that greatly increases the chance of a serious adverse event
Precaution

- A condition in a recipient that may increase the chance or severity of an adverse event

- May compromise the ability of the vaccine to produce immunity

- Might cause diagnostic confusion
Permanent Contraindications

- Severe allergic reaction to a prior dose of vaccine or to a vaccine component
Permanent Contraindications

- **Rotavirus vaccines only**
  - Severe Combined Immunodeficiency disease (SCID)
  - History of intussusception

- **Pertussis vaccines only**
  - Encephalopathy not due to another identifiable cause occurring within 7 days of pertussis vaccination
## Contraindications and Precautions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Live</th>
<th>Inactivated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergy to component</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>---</td>
<td>C</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>C</td>
<td>V*</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>C</td>
<td>V</td>
</tr>
<tr>
<td>Moderate/severe illness</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>Recent blood product</td>
<td>P**</td>
<td>V</td>
</tr>
</tbody>
</table>

C=contraindication
P=precaution
V=vaccinate if indicated
*Except HPV
**MMR and varicella-containing (except zoster vaccine and LAIV)
TABLE 4-1. Contraindications and precautions\(^{(a)}\) to commonly used vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Citation</th>
<th>Contraindications</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>DT, Td</td>
<td>(4)</td>
<td>Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component.</td>
<td>GBS &lt;6 weeks after previous dose of tetanus-toxoid-containing vaccine. History of Arthus-type hypersensitivity reactions after a previous dose of diphtheria-toxoid—containing or tetanus-toxoid-containing vaccine; defer vaccination until at least 10 years have elapsed since the last tetanus-toxoid-containing vaccine. Moderate or severe acute illness with or without fever.</td>
</tr>
<tr>
<td>DTaP</td>
<td>(38)</td>
<td>Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component. Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures), not attributable to another identifiable cause, within 7 days of administration of previous dose of DTP or DTaP.</td>
<td>Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, progressive encephalopathy; defer DTaP until neurologic status clarified and stabilized. Temperature of ≥105°F (≥40.5°C) within 48 hours after vaccination with a previous dose of DTP or DTaP. Collapse or shock-like state (i.e., hypotonic hyporesponsive episode) within 48 hours after receiving a previous dose of DTP/DTaP. Seizure ≤3 days after receiving a previous dose of DTP/DTaP. Persistent, intractable crying lasting ≥3 hours within 48 hours after receiving a previous dose of DTP/DTaP.</td>
</tr>
</tbody>
</table>

Included in Pink Book Appendix A-28-30
Vaccination During Pregnancy

- Live vaccines should not be administered to women known to be pregnant.

- In general, inactivated vaccines may be administered to pregnant women for whom they are indicated.

- HPV vaccine should be deferred during pregnancy.
Vaccination During Pregnancy

- Inactivated vaccines
  - Routine
    - Influenza – any trimester
    - Tdap – 27 to 36 weeks
  - Vaccinate if indicated (HepA, HepB, MenACWY)
  - Withhold (HPV)
  - Vaccinate if increased risk (all others except PCV13, Hib, MenB)
Vaccination of Immunocompromised Persons

- Live vaccines should not be administered to severely immunocompromised persons.

- Persons with isolated B-cell deficiency may receive varicella vaccine.

- Inactivated vaccines are safe to use in immunocompromised persons, but the response to the vaccine may be decreased.
Immunosuppression

- **Disease**
  - Congenital immunodeficiency
  - Leukemia or lymphoma
  - Generalized malignancy

- **Cancer Therapy**
  - Alkylating agents
  - Antimetabolites
  - Radiation
Immunosuppressive Drugs

- Immune mediators
- Immune modulators
- Iso-antibodies (therapeutic monoclonal antibodies)
  - Antitumor necrosis factor agents
Corticosteroids and Immunosuppression

- The amount or duration of corticosteroid therapy needed to increase adverse event risk is not well-defined.

- Dose generally believed to be a concern:
  - 20 mg or more/day of prednisone for 2 weeks or longer
  - 2 mg/kg per day or more of prednisone for 2 weeks or longer
Corticosteroids and Immunosuppression

- Does NOT apply to aerosols, topical, alternate-day, short courses (less than 2 weeks), physiologic replacement schedules
- Delay live vaccines for at least 1 month after discontinuation of high-dose therapy
Vaccination of Immunosuppressed Persons

Safety:

- Immunocompromised persons are at increased risk of adverse events following live vaccines.

- Live vaccines may be administered at least 3 months following termination of chemotherapy (at least 1 month after high-dose steroid use of 2 weeks or more).

- LAIV, MMR, varicella, and rotavirus vaccines may be administered to susceptible household and other close contacts.
Vaccination of Immunosuppressed Persons

- Safety and efficacy

- Anti-tumor necrosis factor inhibitors
  - Wait 3 months after stopping medication before administering live vaccines
  - Do not initiate medication until 1 months after the live vaccine

- Other iso-antibodies (e.g., anti-B cell antibodies aka lymphocyte depleting agents)
  - Some experts recommend up to 6 months
Persons with HIV Infection

- Persons with HIV/AIDS are at increased risk for complications of measles, varicella, influenza, and pneumococcal disease.
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Asymptomatic</th>
<th>Symptomatic*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varicella</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Zoster</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>MMR</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>MMRV</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>LAIV</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>Consider</td>
<td>Consider</td>
</tr>
<tr>
<td>Yellow Fever</td>
<td>Consider</td>
<td>No</td>
</tr>
</tbody>
</table>

Yes=vaccinate   No=do not vaccinate

*See specific ACIP recommendations for details.