The Use of Combination Vaccines in the United States

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Combination Vaccine

• Definition: a product that can be divided equally into independently available routine vaccines.
FDA Licensed Combination Vaccines

- DTaP-HepB-IPV – Pediarix (2002)
- MMRV – ProQuad (2005)
- DTaP-IPV – Kinrix (2008)
- DTaP-IPV/Hib – Pentacel (2008)
- DTaP-IPV – Quadracel (2015)
Combination Vaccine
Advantages
Reduce the Number of Injections

- To meet childhood immunization schedule can require close to 30 injections plus annual influenza vaccine.

- As many as nine vaccines could be recommended at a single visit: MMR, varicella, Hib, PCV13, pediatric diphtheria and tetanus toxoids and acellular pertussis [DTaP], inactivated poliovirus [IPV], hepatitis A, hepatitis B [HepB], and influenza vaccines.

- If wrong site is used, vaccine could be less effective (HepB, Rabies) or more reactogenic (most adjuvant-containing vaccines erroneously injected subcutaneously).
Improve Vaccination Coverage

- Retrospective analysis of 18,821 Georgia infants
  - Receipt of either Hib-HepB or DTaP-HepB-IPV associated with increased coverage of DTaP, IPV, 4:3:1, 4:3:1:3, and 3:3:3 series (rise was 3-6 % points)

Improve Vaccination Timeliness

- **Germany** – 2701 children – Hib, IPV, HepB vaccines given 0.3 – 0.9 months early if combination products used

- **Georgia, USA** - 5552 children– 66% vs 61% on-time rate for DTaP, IPV, Hib, HepB and other series if DTaP-HepB-IPV used

Impact of Combination Vaccines on Vaccine Completion and Compliance - 2012

2012, National Immunization survey, Human Vaccines and Immunotherapeutics, 2017
Reduced Shipping and Storage Costs

- Storage space = storage cost
- Limited storage space requires purchase of new units
- Providers that purchase single components and combinations store them all in the freezer (MMR does not need to be stored there).
Reducing the Cost of Extra Health-care Visits

- 1999 National Immunization Survey data - 71% of children receive a maximum of four immunizations per visit
- Risk exists that some immunizations would need to be deferred
Disadvantages of Combination Vaccines
Increased Risk of Adverse Reactions

- ~2 fold higher risk of febrile seizures in children 12-23 months old vaccinated with MMRV instead of MMR + Var

- Observational study of 3938 6 – 10 week old infants showed an infant receiving Pediarix 6.8 times more likely to receive a fever work-up than receiving component vaccines

Confusion and Uncertainty

- Patients are seen by different providers who have different contracts for different types of vaccines
  - 5.5% of children see more than one provider (95% of children have a usual place of health-care) NCHS. Summary Health Statistics for U.S. children: National Health Interview Survey 2007)

- Contracts may limit the choice of formulation (single component vs combination)

- Providers may administer an extra antigen or skip an essential antigen
Acceptance of Combination Vaccines by Pediatricians

- US pediatricians survey on use of combination vaccines
  - Regard as safe (99%), effective (99%), and increased coverage (84%)
  - In use by 78% - DTaP-HepB-IPV (70%)
  - Inadequate reimbursement hinders use (20%)
  - Factors associated with use - large practice, public insurance, VFC participation, adequate support for administration
  - Providers receive on average $23 less for providing combination vaccines
## CDC Price List Selected Vaccines- 2018

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>VFC price /dose</th>
<th>Private price/dose</th>
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</thead>
<tbody>
<tr>
<td>Pediarix DtaP-HepB-IPV</td>
<td>$57.97</td>
<td>$76.95</td>
</tr>
<tr>
<td>DtaP, HepB, IPV</td>
<td>$45.52</td>
<td>$79.07</td>
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<tr>
<td>Pentacel DTaP-IPV-Hib</td>
<td>$58.33</td>
<td>$92.58</td>
</tr>
<tr>
<td>DtaP, IPV, Hib</td>
<td>$41.14</td>
<td>$66.57</td>
</tr>
<tr>
<td>Twinrix- HepA, HepB</td>
<td>$56.76</td>
<td>$101.00</td>
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<tr>
<td>HepA, HepB</td>
<td>$55.62</td>
<td>124.80</td>
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</tbody>
</table>

Parent Perspectives on Combination and Single Antigen Vaccines

- 86% of children (age 24-35 mos.) received at least one combination vaccine
- Most parents believe combination vaccines are safe (77%)
- Recipients of single antigen vaccine tend to be from families above poverty line, college educated, married parents profile of parents with vaccine hesitancy
- Reasons for vaccine hesitancy
  - Number of injections
  - Immune system overload
  - Adverse events – immediate (pain, fever), long term (autism)
- Parents willing to pay more for less acute adverse events, fewer injections and better community vaccine coverage
- In 2012, of parents, 5.4% delayed and 5.0% refused vaccines for children 6 years of age

The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Considerations should include provider assessment*, patient preference, and the potential for adverse events.

*Provider assessment should include number of injections, vaccine availability, vaccination status, likelihood of improved coverage, likelihood of patient return visits, and cost and storage considerations.

Approved June 2009 ACIP meeting
Aug 2009, Provisional Recs, ACIP
Hepatitis B Vaccine Schedule

- **Birth Dose (Single antigen HepB vaccine only):**
  - Mother is HBsAg-: 1 dose < 24 hours of birth
  - Mother is HBsAg+: HepB/0.5 mL HBIG < 12 hours of birth, regardless of birth weight.; test mother for HBV DNA
  - Mother’s HBsAg status unknown: HepB <12 hours of birth, regardless of birth weight.

- **Routine Infant Series:**
  - Complete series: 3 doses at 0, 1–2, and 6–18 months. (single antigen vaccine before 6 weeks.

- Four doses of vaccine is permitted when combination vaccine is used after birth dose.

- Minimum age for the final (3rd or 4th) dose: 24 weeks.

- Minimum Intervals: Dose 1 to Dose 2: 4 weeks / Dose 2 to Dose 3: 8 weeks / Dose 1 to Dose 3: 16 weeks. (When 4 doses are given, substitute “Dose 4” for “Dose 3” in these calculations.)
Three Dose Completion of Hepatitis B Vaccine for Children 19-35 months of Age
Pediarix®

- DTaP – Hep B – IPV combination
- Approved for 3 doses at 2, 4 and 6 months
- Not approved for booster doses (dose 4 or 5)
- Licensed for children 6 weeks through 6 years of age (catch-up of doses 1, 2, 3)
- Minimum Intervals determined by Hep B component
The “Pediarix Challenge”

- Off-schedule administration could lead to 2 potential invalid doses:
  - Hepatitis B birth dose (HepB1)
  - Pediarix at 2 months (HepB2)
  - Pediarix at 5 months (invalid HepB-age younger than 24 weeks)
  - Pediarix at 6 months (invalid HepB-interval since last dose less than 8 weeks)

- CDC does NOT recommend a 5th dose of Hepatitis B vaccine in this situation
Summary

• Combination vaccines are recommended and well accepted

• Use associated with improved coverage and compliance

• Well accepted by providers and parents

• Guidance and education needed to harmonize use of combination and single antigen vaccines
## Combination Vaccines

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
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<tbody>
<tr>
<td>↓ number of injections</td>
<td>Higher costs to providers and perhaps lower reimbursement</td>
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<tr>
<td>↑ timely coverage</td>
<td>Unnecessary doses</td>
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<tr>
<td>↓ costs of stocking &amp; administering separate vaccines</td>
<td>Potential for increased adverse reactions (e.g. fever with MMRV vaccine + TaP-HepB-IPV)</td>
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<td>↓ costs of extra healthcare visits</td>
<td>Shorter self life</td>
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<td>Facilitate introduction of new vaccines &amp; recommendations</td>
<td>Confusion regarding scheduling</td>
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</table>
Figure 1. Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger—United States, 2018.

(FOR THOSE WHO FALL BEHIND OR START LATE, SEE THE CATCH-UP SCHEDULE [FIGURE 2].)

These recommendations must be read with the footnotes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars in Figure 1. To determine minimum intervals between doses, see the catch-up schedule (Figure 2). School entry and adolescent vaccine age groups are shaded in gray.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Birth</th>
<th>1 mo</th>
<th>2 mos</th>
<th>4 mos</th>
<th>6 mos</th>
<th>8 mos</th>
<th>12 mos</th>
<th>16 mos</th>
<th>18 mos</th>
<th>19-23 mos</th>
<th>2-3 yrs</th>
<th>4-6 yrs</th>
<th>7-10 yrs</th>
<th>11-12 yrs</th>
<th>13-15 yrs</th>
<th>16 yrs</th>
<th>17-18 yrs</th>
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<tr>
<td>Hepatitis B ( HepB)</td>
<td>1st dose</td>
<td>2nd dose</td>
<td>3rd dose</td>
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<tr>
<td>Rotavirus^A (RV; RV1-2 dose series)</td>
<td>1st dose</td>
<td>2nd dose</td>
<td>(See footnote 1)</td>
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<td>Diphtheria, tetanus &amp; acellular pertussis (DTaP) (Diph-5+ yrs)</td>
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<td>2nd dose</td>
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<td>Hemophagocytic lymphohistiocytosis (HLH)</td>
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<td>Pneumococcal conjugate (PCV13)</td>
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<td>2nd dose</td>
<td>3rd dose</td>
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<td>Inactivated poliovirus (IPV &lt; 18 yrs)</td>
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<td>3rd dose</td>
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<td>Influenza^A (IV)</td>
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<td>Annual vaccination (IV1 or 2 doses)</td>
<td>Annual vaccination (IV) 1 dose only</td>
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<td>Measles, mumps, rubella (MMR)</td>
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<td>Varicella (VZV)</td>
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<td>Hepatitis A^B ( HepA)</td>
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<td>2nd dose series See footnote 10</td>
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<td>Tetanus, diphtheria &amp; acellular pertussis (Tdap)</td>
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<td>1st dose</td>
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<td>Human papillomavirus (HPV)</td>
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<td>Meningococcal B^D</td>
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NOTE: The above recommendations must be read along with the footnotes of this schedule.