The Use of Combination Vaccines in the United States

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CDC
Immunization

Combination Vaccine

- Definition: a product that can be divided equally into independently available routine vaccines.

FDA Licensed Combination Vaccines

- HepA-HepB – Twinrix (2001)
- 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)

- Marshall GS, Happe LE, Lunacsek OE et. Al. Pediatr Infect Dis J 2007. 26:496-500, 2007.

Improve Vaccination Timeliness

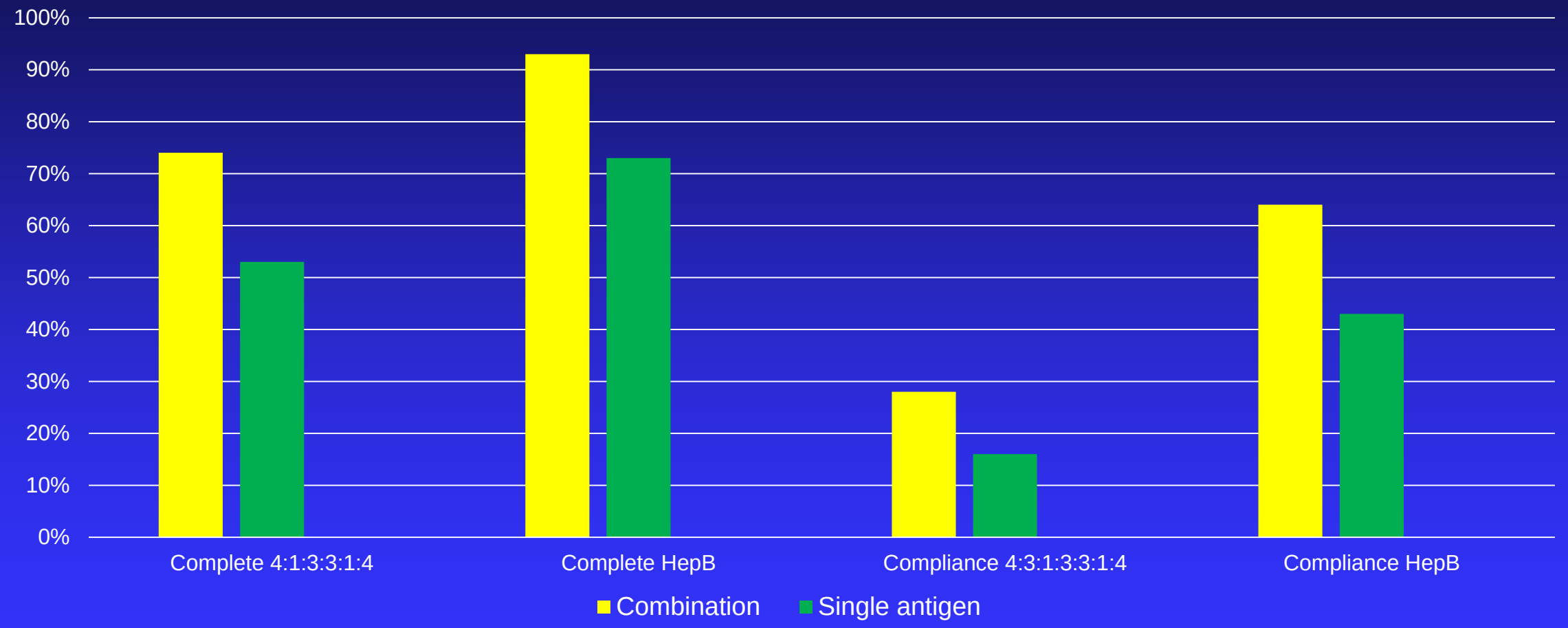
- Germany – 2701 children – Hib, IPV, HepB vaccines given 0.3 – 0.9 months early if combination products used

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

- Kalies H, Grote V, Verstraeten T, et al. The use of combination vaccines has improved timeliness of vaccination in children. Pediatr Infect Dis J. 2006;25:507–512

1. Happe LE, Lunacsek OE, Kruzikas DT, et al. Impact of a pentavalent combination vaccine on immunization timeliness in a state medicaid population. Pediatr Infect Dis J. 2009; 28:98-101.

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

- MMWR March 14,2008 57; Thompson LA, Irigoyen M Matiz LA, et al. The impact of DTaP-IPV-HB vaccine on use of health services for young infants. Pediatr Infect Dis J. 2006;25:826-831.

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

Vaccine	VFC price /dose	Private price/dose
Pediarix DtaP-HepB-IPV	$57.97	$76.95
DtaP, HepB, IPV	$45.52	$79.07
Pentacel DTaP-IPV-Hib	$58.33	$92.58
DtaP, IPV, Hib	$41.14	$66.57
Twinrix- HepA, HepB	$56.76	$101.00
HepA, HepB	$55.62	124.80

https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.htm

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

Kurosky , SK, Human Vaccine Immunotherapeutics, 2017. Frew Vaccine 2016, Gidengil C, Vaccine 2012.

CDC/ACIP Recommendations for Combination Vaccines

- 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.

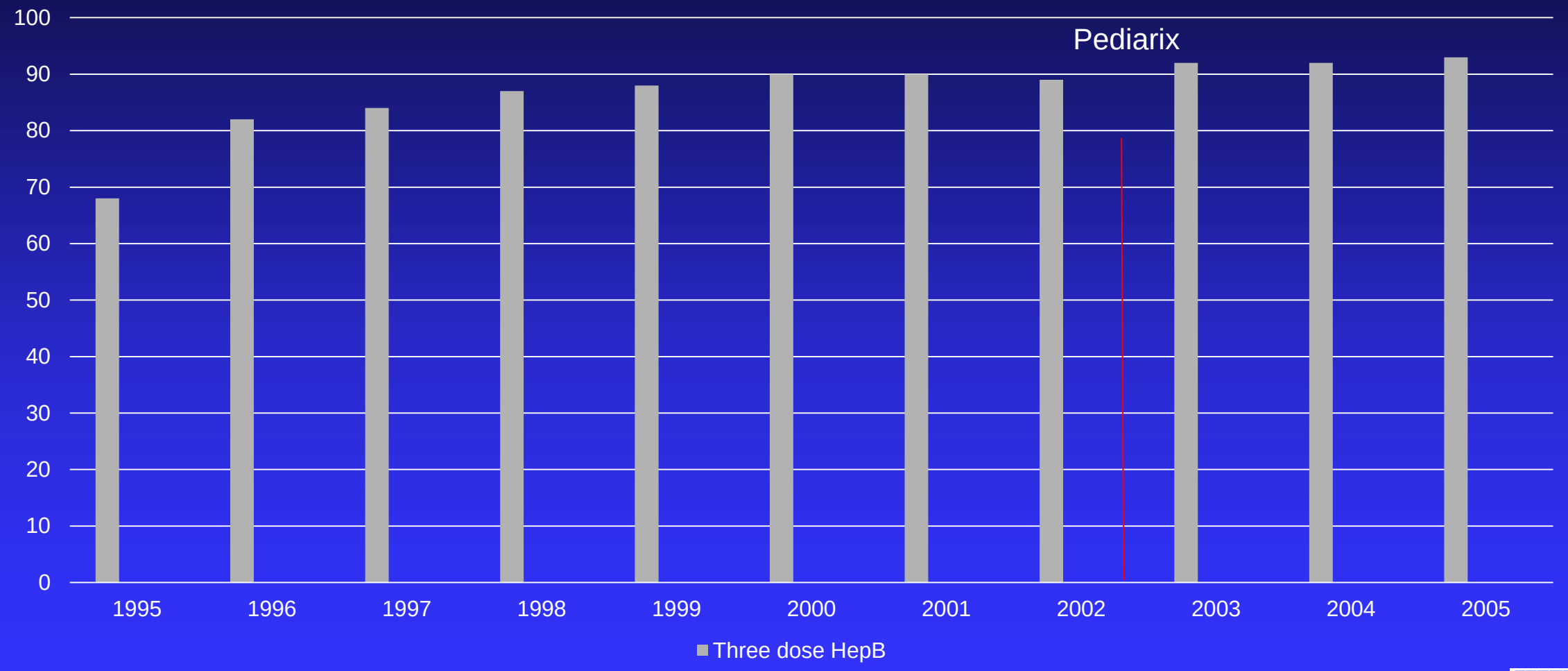
- Routine Infant Series:
- •Complete series: 3 doses at 0, 1–2, and 6–18 months. (single antigen vaccine before 6 weeks.

- 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)
- Mininum 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

Pros	Cons
↓ number of injections	Higher costs to providers and perhaps lower reimbursement
↑ timely coverage	Unnecessary doses
↓ costs of stocking & administering separate vaccines	Potential for increased adverse reactions (e.g. fever with MMRV vaccine + TaP-HepB-IPV)
↓ costs of extra healthcare visits	Shorter self life
Facilitate introduction of new vaccines & recommendations	Confusion regarding scheduling

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.

Vaccine	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos	18 mos	19-23 mos	2-3 yrs	4-6 yrs	7-10 yrs	11-12 yrs	13-15 yrs	16 yrs	17-18 yrs
Hepatitis B[1] (HepB)	1st dose	2nd dose			3rd dose												
Rotavirus[2] (RV) RV1 (2-dose series); RV5 (3-dose series)			1st dose	2nd dose	See footnote 2												
Diphtheria, tetanus, & acellular pertussis[3] (DTaP: <7 yrs)			1st dose	2nd dose	3rd dose			4th dose				5th dose					
Haemophilus influenzae type b[4] (Hib)			1st dose	2nd dose	See footnote 4		3rd or 4th dose, See footnote 4										
Pneumococcal conjugate[5] (PCV13)			1st dose	2nd dose	3rd dose		4th dose										
Inactivated poliovirus[6] (IPV: <18 yrs)			1st dose	2nd dose	3rd dose							4th dose					
Influenza[7] (IIV)					Annual vaccination (IIV) 1 or 2 doses									Annual vaccination (IIV) 1 dose only			
Measles, mumps, rubella[8] (MMR)					See footnote 8		1st dose					2nd dose					
Varicella[9] (VAR)							1st dose					2nd dose					
Hepatitis A[10] (HepA)							2-dose series, See footnote 10										
Meningococcal[11] (MenACWY-D ≥9 mos; MenACWY-CRM ≥2 mos)			See footnote 11											1st dose		2nd dose	
Tetanus, diphtheria, & acellular pertussis[13] (Tdap: ≥7 yrs)														Tdap			
Human papillomavirus[14] (HPV)														See footnote 14			
Meningococcal B[12]														See footnote 12			
Pneumococcal polysaccharide[5] (PPSV23)											See footnote 5						

Range of recommended ages for all children

Range of recommended ages for catch-up immunization

Range of recommended ages for certain high-risk groups

Range of recommended ages for non-high-risk groups that may receive vaccine, subject to individual clinical decision making

No recommendation

NOTE: The above recommendations must be read along with the footnotes of this schedule.