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*Recommendations
and
Reports*

Inside: Continuing Education Examination

Combination Vaccines for Childhood Immunization

**Recommendations of the Advisory Committee on
Immunization Practices (ACIP), the American
Academy of Pediatrics (AAP), and the American
Academy of Family Physicians (AAFP)**

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Disease Control and Prevention (CDC)
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Abbreviations Used in This Report*

DT	Diphtheria and tetanus toxoids vaccine (for children)
DTaP	Diphtheria and tetanus toxoids and acellular pertussis vaccine
DTaP-Hib	Diphtheria and tetanus toxoids and acellular pertussis and <i>Haemophilus influenzae</i> type b vaccine
DTP	Diphtheria and tetanus toxoids and pertussis vaccine (unspecified pertussis antigens)
DTP-Hib	Diphtheria and tetanus toxoids and pertussis and <i>Haemophilus influenzae</i> type b vaccine (unspecified pertussis antigens)
DTwP	Diphtheria and tetanus toxoids and whole-cell pertussis vaccine
DTwP-Hib	Diphtheria and tetanus toxoids and whole-cell pertussis and <i>Haemophilus influenzae</i> type b vaccine
HepA	Hepatitis A vaccine
HepB	Hepatitis B vaccine
Hib	<i>Haemophilus influenzae</i> type b conjugate vaccine
PRP-OMP Hib	polyribosylribitol phosphate polysaccharide conjugated to a meningococcal outer membrane protein
PRP-T Hib	polyribosylribitol phosphate polysaccharide conjugated to tetanus toxoid
HbOC Hib	oligosaccharides conjugated to diphtheria CRM ₁₉₇ toxin protein
PRP-D Hib	polyribosylribitol phosphate polysaccharide conjugated to diphtheria toxoid
Hib-HepB	<i>Haemophilus influenzae</i> type b and hepatitis B vaccine
Hib-HepB-IPV	<i>Haemophilus influenzae</i> type b, hepatitis B, and trivalent inactivated polio vaccine
INF	Influenza vaccine
IPV	Trivalent inactivated polio vaccine (killed Salk type)
Me	Measles vaccine
Me-Rub	Measles and rubella vaccine
MenCon	Meningococcal (<i>Neisseria meningitidis</i>) conjugate vaccine
MenPS	Meningococcal (<i>Neisseria meningitidis</i>) polysaccharide vaccine
MMR	Measles-mumps-rubella vaccine
MMR-Var	Measles-mumps-rubella and varicella vaccine
Mu	Mumps vaccine
Mu-Rub	Mumps and rubella vaccine
OPV	Trivalent oral polio vaccine (live Sabin type)
PnuCon	Pneumococcal (<i>Streptococcus pneumoniae</i>) conjugate vaccine
PnuPS	Pneumococcal (<i>Streptococcus pneumoniae</i>) polysaccharide vaccine
Rub	Rubella vaccine
Rv	Rotavirus vaccine
Td	Tetanus and diphtheria toxoids vaccine (for adolescents and adults)
TT	Tetanus toxoid vaccine
Var	Varicella (chickenpox) vaccine

*Excludes some pentavalent and larger combinations listed in Appendix A. As of publication date, some vaccine combinations listed are not licensed or approved for persons of all ages in the United States.

**Product Brand Names and Manufacturers/Distributors
for Principal Childhood Vaccine Types**

DTaP diphtheria and tetanus toxoids and acellular pertussis vaccine	ACEL-IMUNE® (WLV) Certiva™ (NAV, distributed by ALI) Infanrix® (SBB, distributed by SB) Tripedia® (CON, distributed by PMC)
DTaP-Hib diphtheria and tetanus toxoids and acellular pertussis and <i>Haemophilus influenzae</i> type b vaccine	TriHIBit®* (ActHIB® Hib reconstituted with Tripedia® DTaP; distributed by PMC)
DTwP diphtheria and tetanus toxoids and whole-cell pertussis vaccine	Tri-Immunol® (WLV) [†] (Generic products from other manufacturers)
DTwP-Hib diphtheria and tetanus toxoids and whole-cell pertussis and <i>Haemophilus influenzae</i> type b vaccine	ActHIB® Hib reconstituted with DTwP (CON; distributed by PMC) TETRAMUNE® (WLV)
HepA hepatitis A vaccine	HAVRIX® (SBB, distributed by SB) VAQTA® (MRK)
HepB hepatitis B vaccine	ENGERIX-B® (SBB, distributed by SB) RECOMBIVAX HB® (MRK)
Hib <i>Haemophilus influenzae</i> type b conjugate vaccine HbOC – oligosaccharides conjugated to diphtheria CRM ₁₉₇ toxin protein PRP-OMP – polyribosylribitol phosphate polysaccharide conjugated to a meningococcal outer membrane protein PRP-T – polyribosylribitol phosphate polysaccharide conjugated to tetanus toxoid PRP-D – polyribosylribitol phosphate polysaccharide conjugated to diphtheria toxoid	HibTITER® (WLV) PedvaxHIB® (MRK) ActHIB® (PMSV, distributed by CON, PMC) OmniHIB™ (PMSV, distributed by SB) ProHIBit® (CON, distributed by PMC)
Hib-HepB <i>Haemophilus influenzae</i> type b and hepatitis B vaccine	COMVAX® (Hib component = PRP-OMP) (MRK)
IPV trivalent inactivated polio vaccine (killed Salk type)	IPOL® (PMSV, distributed by CON, PMC)
MMR measles-mumps-rubella vaccine	M-M-R® II (MRK)
OPV trivalent oral polio vaccine (live Sabin type)	Orimune® (WLV)
Rv rotavirus vaccine (live, oral, tetravalent)	RotaShield® (WLV)
Var Varicella (chickenpox) vaccine	VARIVAX® (MRK)

* As of April 10, 1999, TriHIBit® was licensed only for the fourth dose recommended at age 15–18 months in the vaccination series.

[†] Manufacture discontinued.

Abbreviations: ALI=Ross Products Division, Abbott Laboratories Inc.; CON=Connaught Laboratories, Inc.; MRK=Merck & Co., Inc.; NAV=North American Vaccine, Inc.; PMC=Pasteur Mérieux Connaught; PMSV=Pasteur Mérieux Sérums & Vaccins, S.A.; SBB=SmithKline Beecham Biologicals; SB=SmithKline Beecham Pharmaceuticals; WLV=Lederle Laboratories Division of American Cyanamid Company (marketed by Wyeth-Lederle Vaccines, Wyeth-Ayerst Laboratories).

Combination Vaccines for Childhood Immunization

Recommendations of the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP)

Summary

An increasing number of new and improved vaccines to prevent childhood diseases are being introduced. Combination vaccines represent one solution to the problem of increased numbers of injections during single clinic visits. This statement provides general guidance on the use of combination vaccines and related issues and questions.

To minimize the number of injections children receive, parenteral combination vaccines should be used, if licensed and indicated for the patient's age, instead of their equivalent component vaccines. Hepatitis A, hepatitis B, and Haemophilus influenzae type b vaccines, in either monovalent or combination formulations from the same or different manufacturers, are interchangeable for sequential doses in the vaccination series. However, using acellular pertussis vaccine product(s) from the same manufacturer is preferable for at least the first three doses, until studies demonstrate the interchangeability of these vaccines. Immunization providers should stock sufficient types of combination and monovalent vaccines needed to vaccinate children against all diseases for which vaccines are recommended, but they need not stock all available types or brand-name products. When patients have already received the recommended vaccinations for some of the components in a combination vaccine, administering the extra antigen(s) in the combination is often permissible if doing so will reduce the number of injections required.

To overcome recording errors and ambiguities in the names of vaccine combinations, improved systems are needed to enhance the convenience and accuracy of transferring vaccine-identifying information into medical records and immunization registries. Further scientific and programmatic research is needed on specific questions related to the use of combination vaccines.

INTRODUCTION

The introduction of vaccines for newly preventable diseases poses a challenge for their incorporation into an already complex immunization schedule. To complete the 1999 Recommended Childhood Immunization Schedule in the United States (1,2), a minimum of 13 separate injections are needed to immunize a child from birth to age 6 years, using vaccines licensed in the United States as of April 10, 1999. During some office or clinic visits, the administration of three or four separate injections can be indicated.

Combination vaccines merge into a single product antigens that prevent different diseases or that protect against multiple strains of infectious agents causing the same

disease. Thus, they reduce the number of injections required to prevent some diseases. Combination vaccines available for many years include diphtheria and tetanus toxoids and whole-cell pertussis vaccine (DTwP); measles-mumps-rubella vaccine (MMR); and trivalent inactivated polio vaccine (IPV). Combinations licensed in recent years in the United States include diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) (3–6), DTwP-*Haemophilus influenzae* type b (Hib) vaccine (DTwP-Hib) (7,8), DTaP-Hib* (9), and Hib-hepatitis B (HepB) vaccine (Hib-HepB) (10). In the future, combination vaccines might include increasing numbers of components in different arrays to protect against these and other diseases, including hepatitis A, *Neisseria meningitidis*, *Streptococcus pneumoniae*, and varicella (Appendix A) (11).

Combination vaccines have some drawbacks. Chemical incompatibility or immunologic interference when different antigens are combined into one vaccine could be difficult to overcome (12–16). Vaccine combinations that require different schedules might cause confusion and uncertainty when children are treated by multiple vaccine providers who use different products. The trend to develop combination products could encourage vaccine companies to merge to acquire the needed intellectual property (17). Competition and innovation might be reduced if companies with only a few vaccine antigens are discouraged from developing new products.

This report, published simultaneously by the Advisory Committee on Immunization Practices (ACIP) (18), the American Academy of Pediatrics (AAP) (19) and the American Academy of Family Physicians (AAFP) (20), provides general recommendations for the optimal use of existing and anticipated parenteral combination vaccines, along with relevant background, rationale, and discussion of questions raised by the use of these products. Principal recommendations are classified by the strength and quality of evidence supporting them (Appendix B) (21–24).

PREFERENCE FOR COMBINATION VACCINES

The use of licensed combination vaccines is preferred over separate injection of their equivalent component vaccines. Only combinations approved by the U.S. Food and Drug Administration (FDA) should be used.

Rationale

The use of combination vaccines is a practical way to overcome the constraints of multiple injections, especially for starting the immunization series for children behind schedule. The use of combination vaccines might improve timely vaccination coverage. Some immunization providers and parents object to administering more than two or three injectable vaccines during a single visit because of a child's fear of needles and pain (25–30) and because of unsubstantiated concerns regarding safety (31,32).

Other potential advantages of combination vaccines include a) reducing the cost of stocking and administering separate vaccines, b) reducing the cost for extra health-care visits, and c) facilitating the addition of new vaccines into immunization

*As of April 10, 1999, DTaP-Hib vaccine was licensed only for the fourth dose recommended at age 15–18 months in the vaccination series.

programs. The price of a new combination vaccine can sometimes exceed the total price of separate vaccines for the same diseases. However, the combination vaccine might represent a better economic value if one considers the direct and indirect costs of extra injections, delayed or missed vaccinations, and additional handling and storage (11).

Combining Separate Vaccines Without FDA Approval

Immunization providers should not combine separate vaccines into the same syringe to administer together unless such mixing is indicated for the patient's age on the respective product label inserts approved by the FDA. The safety, immunogenicity, and efficacy of such unlicensed combinations are unknown (33).

INTERCHANGEABILITY OF VACCINE PRODUCTS

In general, vaccines from different manufacturers that protect against the same disease may be administered interchangeably in sequential doses in the immunization series for an individual patient (e.g., hepatitis A [HepA], HepB, and Hib). However, until data supporting interchangeability of acellular pertussis vaccines (e.g., DTaP) are available, vaccines from the same manufacturer should be used, whenever feasible, for at least the first three doses in the pertussis series. Immunization providers who cannot determine which DTaP vaccine was previously administered, or who do not have the same vaccine, should use any of the licensed acellular pertussis products to continue the immunization series.

Interchangeability of Formulations

The FDA generally licenses a combination vaccine based on studies indicating that the product's immunogenicity (or efficacy) and safety are comparable with or equivalent to monovalent or combination products licensed previously (16,34). FDA approval also generally indicates that a combination vaccine may be used interchangeably with monovalent formulations and other combination products with similar component antigens produced by the same manufacturer to continue the vaccination series. For example, DTaP, DTaP-Hib, and future DTaP-combination vaccines (Appendix A) that contain similar acellular pertussis antigens from the same manufacturer may be used interchangeably, if approved for the patient's age.

Interchangeability of Vaccines From Different Manufacturers

The licensure of a vaccine does not necessarily indicate that interchangeability with products of other manufacturers has been demonstrated. Such data are ascertained and interpreted more easily for diseases with known correlates of protective immunity (e.g., specific antibodies). For diseases without such surrogate laboratory markers, field efficacy (phase III) trials or postlicensure surveillance generally are required to determine protection (35,36).

Diseases With Serologic Correlates of Immunity

Studies of serologic responses that have been correlated with protection against specific diseases support the interchangeability of vaccines from different manufacturers for HepA, HepB, and Hib.

Preliminary data indicate that the two hepatitis A vaccine products currently licensed in the United States (37) may be used interchangeably (38) (Merck & Co., Inc., unpublished data, 1998). Hepatitis B vaccine products (i.e., HepB and Hib-HepB if age-appropriate) also may be interchanged for any doses in the hepatitis B series (39).

Based on subsequent data (40–42), the guidelines for *Haemophilus influenzae* type b disease (7,43) were updated in the 1998 Recommended Childhood Immunization Schedule (44–47) to indicate that different Hib vaccine products from several manufacturers may be used interchangeably for sequential doses of the vaccination series. A PRP-OMP Hib (Hib vaccine with a polyribosylribitol phosphate polysaccharide conjugated to a meningococcal outer membrane protein) or a PRP-OMP Hib-HepB vaccine might be administered in a series with HbOC Hib (Hib vaccine with oligosaccharides conjugated to diphtheria CRM₁₉₇ toxin protein) or with PRP-T Hib (polyribosylribitol phosphate polysaccharide conjugated to tetanus toxoid). In such cases, the recommended number of doses to complete the series is determined by the HbOC or PRP-T product, not by the PRP-OMP vaccine (1,2). For example, if PRP-OMP Hib is administered for the first dose at age 2 months and another product is administered at age 4 months, a third dose of any of the licensed Hib vaccines is recommended at age 6 months to complete the primary series.

Diseases Without Serologic Correlates of Immunity

Despite extensive research, no serologic correlates of immunity have been identified for pertussis. Limited data exist concerning the safety, immunogenicity, or efficacy of administering acellular pertussis vaccines (e.g., DTaP or DTaP-Hib) from different manufacturers between the fourth (at age 15–18 months) and fifth (at age 4–6 years) doses in the vaccination series (48). No data are available regarding the interchangeability of acellular pertussis products from different manufacturers for the first three pertussis doses scheduled at ages 2, 4, and 6 months. Thus, use of the same manufacturer's acellular pertussis vaccine product(s) is preferred for at least the first three doses in the series (5,49).

VACCINE SUPPLY

Immunization clinics and providers should maintain a supply of vaccines that will protect children from all diseases specified in the current Recommended Childhood Immunization Schedule (1,2). This responsibility can be fulfilled by stocking several combination and monovalent vaccine products. However, not stocking all available combination and monovalent vaccines or multiple products of each is acceptable.

New and potential combination vaccines can contain different but overlapping groups of antigens (Appendix A). Thus, not all such vaccines would need to be available for the age-appropriate vaccination of children. Those responsible for childhood vaccination can stock several vaccine types and products, or they may continue to stock a limited number, as long as they prevent all diseases recommended in the

Continuing Education Activity Sponsored by CDC

Combination Vaccines for Childhood Immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP)

OBJECTIVE

This *MMWR* provides recommendations and guidance for the use of combination vaccines in children. This statement was developed by working groups and representatives of the ACIP, AAP, and AAFP, who convened in December 1996 and reached consensus in 1998. These recommendations should guide clinical practice for the care of children and help shape future programs and clinical research agendas. Upon completing this educational activity, the reader should understand the advantages and disadvantages of combination vaccines, which products may be interchanged for sequential doses, and the rationale for and limits of administering extra doses of vaccine antigens.

ACCREDITATION

Continuing Medical Education (CME): This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) by CDC. CDC is accredited by the ACCME to provide continuing medical education for physicians. CDC designates this educational activity for a maximum of 1 hour in category 1 credit toward the AMA Physician's Recognition Award.

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EXPIRATION — May 14, 2000

The response form must be completed and returned electronically, by fax, or by mail, **postmarked no later than 1 year from the publication date of this report**, for eligibility to receive continuing education credit.

INSTRUCTIONS

1. Read this *MMWR* (Vol. 48, RR-5), which contains the correct answers to the questions beginning on the next page.
2. Complete all registration information on the response form, including your name, mailing address, phone number, and e-mail address, if available.
3. Indicate whether you are registering for Continuing Medical Education (CME), Continuing Education Unit (CEU), or Continuing Nursing Education (CNE) credit.
4. Select your answers to the questions, and mark the corresponding letters on the response form. To receive continuing education credit, you must answer *all* of the questions. Questions with more than one answer will instruct you to "indicate all that are true."
5. Sign and date the response form.
6. Return the response form, or a photocopy of the form, no later than **May 14, 2000**, to CDC by one of the following methods:

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To receive continuing education credit, please answer all of the following questions.

1. Which of the following are combination vaccines? (Indicate all that are true.)

- A. Hepatitis A vaccine (HepA).
- B. *Haemophilus influenzae* type b vaccine (Hib).
- C. Inactivated polio vaccine (IPV).
- D. Tetanus and diphtheria toxoids vaccine (Td).

2. Which of the following are advantages of using a combination vaccine instead of separate monovalent vaccines for the same diseases? (Indicate all that are true.)

- A. Lower purchase price for the combination compared with the purchase of separate vaccines for the individual components.
- B. Reduced pain and needle phobia caused when multiple injectable vaccines are administered during a single visit.
- C. Decreased handling and stocking compared with separate vaccines.
- D. Facilitation of the introduction of new vaccines into immunization programs.

3. Combining two separate vaccines into the same syringe for administration together is allowable . . . (Indicate all that are true.)

- A. only when a child would otherwise require ≥ 4 injections.
- B. only when FDA-approved for the specific vaccines and age of the child.
- C. only when a child is aged ≥ 12 months.
- D. only when the risk for missed opportunity to vaccinate outweighs the risk for possible adverse reactions.

4. For which of the following vaccines may products from different manufacturers be interchanged routinely for sequential doses in the series for a patient? (Indicate all that are true.)

- A. Hepatitis A vaccine (HepA).
- B. Hepatitis B vaccine (HepB).
- C. *Haemophilus influenzae* type b vaccine (Hib).
- D. Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP).

- 5. Which vaccine antigens have caused local adverse reactions in some cases when administered to persons still immune from prior vaccinations? (*Indicate all that are true.*)**
- A. Measles (Me, or in MMR).
 - B. Tetanus toxoid-containing vaccines.
 - C. Hepatitis B (HepB).
 - D. Pneumococcal polysaccharide vaccine (PnuPS).
- 6. According to 1994 data, the percentage of U.S. children who received vaccinations from two or more immunization providers during the first 2 years of life was . . . (*Choose the one correct answer.*)**
- A. 5%.
 - B. 10%.
 - C. 25%.
 - D. 50%.
- 7. Immunization providers are required by law to document in medical records which of the following information for most vaccines administered to children? (*Indicate all that are true.*)**
- A. Vaccine identity (type and manufacturer or brandname).
 - B. Date of administration.
 - C. Vaccine expiration date.
 - D. Vaccine lot number.
- 8. Strategies that might improve the accuracy and timely availability of the immunization histories of patients include . . . (*Indicate all that are true.*)**
- A. routine questionnaires administered to parents.
 - B. peel-off identification stickers on vaccine vials for use in medical charts.
 - C. barcodes on vaccine packaging, which are then scanned into medical records systems.
 - D. confidential reporting and access to immunization registries.
- 9. Indicate the setting where you work.**
- A. State/local health department.
 - B. Other public health setting.
 - C. Hospital clinic/private practice.

- D. Managed care organization.
- E. Academic institution.
- F. Other.

10. Which best describes your professional activities?

- A. Family practice/general medicine.
- B. Pediatrics.
- C. Laboratory/pharmacy.
- D. Immunization clinic.
- E. Administration/research.
- F. Other.

11. I plan to use these guidelines as the basis for . . . (Indicate all that are true.)

- A. health education materials.
- B. insurance reimbursement policies.
- C. local practice guidelines.
- D. public policy.
- E. other.

12. Each month, approximately how many patients/clients requiring vaccinations do you treat?

- A. None.
- B. 1–5.
- C. 6–15.
- D. 16–25.
- E. ≥ 26 .

13. How much time did you spend reading this report and completing the exam?

- A. ≤ 1 hour.
- B. >1 hour but <2 hours.
- C. ≥ 2 hours but <3 hours.
- D. ≥ 3 hours.

14. Overall, this report met the stated objectives.

- A. Strongly agree.
- B. Agree.
- C. Neither agree nor disagree.
- D. Disagree.
- E. Strongly disagree.

15. The tables and figure are useful.

- A. Strongly agree.
- B. Agree.
- C. Neither agree nor disagree.
- D. Disagree.
- E. Strongly disagree.

16. Overall, the presentation of the report enhanced my ability to understand the material.

- A. Strongly agree.
- B. Agree.
- C. Neither agree nor disagree.
- D. Disagree.
- E. Strongly disagree.

17. These recommendations will affect my practice.

- A. Strongly agree.
- B. Agree.
- C. Neither agree nor disagree.
- D. Disagree.
- E. Strongly disagree.

Answer guide for questions 1-8
1.c,d; 2.b,c,d; 3.b; 4.a,b,c; 5.b,d; 6.c; 7.a,b,d; 8.b,c,d

MMWR RESPONSE FORM for Continuing Education Credit
MMWR Vol. 48/No. RR-5. May 14, 1999

Combination Vaccines for Childhood Immunization: Recommendations of the
Advisory Committee on Immunization Practices (ACIP), the American Academy of
Pediatrics (AAP), and the American Academy of Family Physicians (AAFP)

Fill in the appropriate block(s) to indicate your answer(s).

To receive continuing education credit, you must answer all of the questions.

1. A B C D
2. A B C D
3. A B C D
4. A B C D
5. A B C D
6. A B C D
7. A B C D
8. A B C D
9. A B C D E F
10. A B C D E F
11. A B C D E
12. A B C D E
13. A B C D
14. A B C D E
15. A B C D E
16. A B C D E
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immunization schedule (1,2). Potential advantages of stocking a limited number of vaccines include reducing a) confusion and potential errors when staff must handle redundant products and formulations, b) wastage when less commonly used products expire, c) cold storage capacity requirements, and d) administrative overhead in accounting, purchasing, and handling.

EXTRA DOSES OF VACCINE ANTIGENS

Using combination vaccines containing some antigens not indicated at the time of administration to a patient might be justified when a) products that contain only the needed antigens are not readily available or would result in extra injections and b) potential benefits to the child outweigh the risk of adverse events associated with the extra antigen(s). An extra dose of many live-virus vaccines and Hib or HepB vaccines has not been found to be harmful. However, the risk of adverse reactions might increase when extra doses are administered earlier than the recommended interval for certain vaccines (e.g., tetanus toxoid vaccines and pneumococcal polysaccharide vaccine) (23,50).

General Immunization Practice

Patients commonly receive extra doses of vaccines or vaccine antigens for diseases to which they are immune. For example, some children receiving recommended second or third doses of many vaccines in the routine immunization series will already have immunologic protection from previous dose(s). Because serologic testing for markers of immunity is usually impractical and costly, multiple doses for all children are justified for both clinical and public health reasons to decrease the number of susceptible persons, which ensures high overall rates of protection in the population.

Extra vaccine doses also are sometimes administered when an immunization provider is unaware that the child is already up-to-date for some or all of the antigens in a vaccine (see Improving Immunization Records). During National Immunization Days and similar mass campaigns, millions of children in countries around the world are administered polio vaccine (51,52) and/or measles vaccine (53,54), regardless of prior vaccination status.

Extra Doses of Combination Vaccine Antigens

ACIP, AAP, and AAFP recommend that combination vaccines may be used whenever any components of the combination are indicated and its other components are not contraindicated (1,2). An immunization provider might not have vaccines available that contain only those antigens indicated by a child's immunization history. Alternatively, the indicated vaccines might be available, but the provider nevertheless might prefer to use a combination vaccine to reduce the required number of injections. In such cases, the benefits and risks of administering the combination vaccine with an unneeded antigen should be compared.

Live-Virus Vaccines

Administering an extra dose of live, attenuated virus vaccines to immunocompetent persons who already have vaccine-induced or natural immunity has not been

demonstrated to increase the risk of adverse events. Examples of these include MMR, varicella, rotavirus, and oral polio vaccines.

Inactivated Vaccines

When inactivated (killed) or subunit vaccines (which are often adsorbed to aluminum-salt adjuvants) are administered, the reactogenicity of the vaccine must be considered in balancing the benefits and risks of extra doses. Because clinical experience suggests low reactogenicity, an extra dose of Hib or HepB vaccine may be administered as part of a combination vaccine to complete a vaccination series for another component of the combination. Administration of extra doses of tetanus toxoid-containing vaccines earlier than the recommended intervals can increase the risk of hypersensitivity reactions (55–61). Examples of such vaccines include DTaP, DTaP-Hib, diphtheria and tetanus toxoids for children (DT), tetanus and diphtheria toxoids for adolescents and adults (Td), and tetanus toxoid (TT). Extra doses of tetanus toxoid-containing vaccines might be appropriate in certain circumstances, including for children who received prior DT vaccine and need protection from pertussis (in DTaP) or for immigrants with uncertain immunization histories.

Impact of Reimbursement Policies

Administering extra antigens contained in a combination vaccine, when justified as previously described, is acceptable practice and should be reimbursed on the patient's behalf by indemnity health insurance and managed-care systems. Otherwise, high levels of timely vaccination coverage might be discouraged.

Conjugate Vaccine Carrier Proteins

Some carrier proteins in existing conjugated Hib vaccines (62) also are used as conjugates in new vaccines in development (e.g., for pneumococcal and meningococcal disease) (63). Protein conjugates used in Hib conjugate vaccines include a mutant diphtheria toxin (in HbOC), an outer membrane protein from *Neisseria meningitidis* (in PRP-OMP), and tetanus and diphtheria toxoids (in PRP-T and PRP-D [polyribosyl-ribitol phosphate polysaccharide conjugated to a diphtheria toxoid], respectively). Administering large amounts of tetanus toxoid carrier protein simultaneously with PRP-T conjugate vaccine has been associated with a reduction in the response to PRP (64) (see Future Research and Priorities).

IMPROVING IMMUNIZATION RECORDS

Improving the convenience and accuracy of transferring vaccine-identifying information into medical records and immunization registries should be a priority for immunization programs. Priority also should be given to ensuring that providers have timely access to the immunization histories of their patients.

As new combination vaccines with longer generic names and novel trade names are licensed (Appendix A), problems with accurate recordkeeping in medical charts and immunization registries will likely be exacerbated.

Monitoring Vaccine Safety, Coverage, and Efficacy

All health-care providers are mandated by law to document in each patient's medical record the identity, manufacturer, date of administration, and lot number of certain specified vaccines, including most vaccines recommended for children (65,66). Although such data are essential for surveillance and studies of vaccine safety, efficacy, and coverage, these records are often incomplete and inaccurate. Two major active (67) and passive (68,69) surveillance systems monitoring vaccine safety in the United States have detected substantial rates of missing and erroneous data ($\geq 10\%$) in the recording of vaccine type, brand, or lot number in the medical records of vaccine recipients (CDC, unpublished data, 1997). Similar rates of incomplete and incorrect vaccination medical records were encountered by the National Immunization Survey and the National Health Interview Survey (CDC, unpublished data, 1997).

Patient Migration Among Immunization Providers

Changing immunization providers during the course of a child's vaccination series is common in the United States. The 1994 National Health Interview Survey documented that approximately 25% of children were vaccinated by more than one provider during the first 2 years of life (CDC, unpublished data, 1997). Eligibility for Medicaid and resulting enrollment in Medicaid managed-care health plans tend to be sporadic, with an average duration of 9 months and a median of <12 months in 1993 (Health Care Financing Administration, unpublished data, 1998).

The vaccination records of children who have changed immunization providers are often unavailable and incomplete. Missing or inaccurate information regarding the vaccines received previously might preclude accurate determination of which vaccines are indicated at the time of a visit, resulting in the administration of extra doses.

Strategies for Accurate Vaccine Identification

Potential strategies to improve the accuracy and timely availability of vaccination information include the following:

- Designing and adopting a recommended, nationally standardized, uniform vaccination medical record form. A copy provided to parents could serve as a record of vaccination history for subsequent immunization providers and satisfy school entry requirements. Immunization registries could generate printouts to document vaccinations received from multiple providers and to replace misplaced forms.
- Expanding and coordinating immunization registries, which track vaccinations received by children and make the information available in a convenient and timely manner to parents and authorized immunization providers with a need to know, while protecting confidentiality and privacy.
- Developing technologies, standards, and guidelines to improve the accuracy and convenience of recording and transferring information from the vaccine package or vial into a patient's medical record, compatible with both manual and computerized medical record systems. These methods could include standardized, peel-off identification stickers on vaccine packaging and standardized coding of

vaccine identity, expiration date, and lot number. Machine-readable bar codes following Uniform Code Council standards (70) on vaccine packaging and/or stickers could facilitate accurate electronic transfer of this information into computerized medical record systems and immunization registries.

FUTURE RESEARCH AND PRIORITIES

Further efforts are needed to study and obtain more data on the following key subjects related to combination vaccines:

- The interchangeability of vaccines produced by different manufacturers to prevent the same disease, particularly those that differ in the nature or quantity of one or more component antigens.
- The safety and efficacy of administering combination vaccines to patients who might already be fully immunized for one or more of the components.
- Economic and operations research on a) the frequency of delayed or missed vaccinations because of objections to multiple injections; b) the costs of any increased disease burden caused by such missed vaccinations; c) the costs of extra visits needed to comply with the routine immunization schedule; and d) the administrative overhead and cost of errors and confusion that might result when handling a greater number of products.
- The effects on immunogenicity and safety of simultaneous or repeated exposures to the same proteins used as antigens (e.g., tetanus and diphtheria toxoids) and/or as carrier components in existing and future conjugated vaccines.
- Research to develop and evaluate alternative means of antigen delivery by the mucosal (71,72), parenteral (73), and cutaneous routes (74–77), which would allow new and existing vaccines to be administered less painfully and more safely than with needles and syringes (78–80).

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Appendix A

COMBINATION VACCINES*

Existing Combination Vaccines in the United States, March 1999[†]

▶ 1945	INF		
▶ 1946	DTwP		
▶ 1947	DT		
▶ 1953	Td		
▶ 1955		IPV	
▶ 1963			OPV
▶ 1970			Mu-Rub
▶ 1971			Me—Rub
▶ 1971			M M R
▶ 1973			Me-Mu
▶ 1975			MenPS
▶ 1979			PnuPS
▶ 1991	DTaP		
▶ 1993	DTwP-Hib		
▶ 1996	DTaP-Hib		
▶ 1996		Hib-HepB	
▶ 1998			Rv

Potential Combination Vaccines

▶			PnuCon
▶			MenCon
▶		MMR—Var	
▶	DTaP—HepB		
▶	DTaP—IPV		
▶	DTaP—		PnuCon
▶	DTaP—		MenCon
▶	Hib—		PnuCon
▶	Hib—		MenCon
▶	HepB—HepA		
▶	IPV—		PnuCon
▶			MenCon—PnuCon
▶	DTaP—Hib—HepB		
▶	DTaP—Hib—IPV		
▶	DTaP—HepB—IPV		
▶	DTaP—Hib—		PnuCon
▶	DTaP—		MenCon—PnuCon
▶	Hib—HepB—IPV		
▶	Hib—		MenCon—PnuCon
▶	DTaP—Hib—HepB—IPV		
▶	DTaP—Hib—		MenCon—PnuCon
▶	Hib—IPV—		MenCon—PnuCon
▶	DTaP—Hib—HepB—IPV—HepA		

*Combination vaccines are defined as those containing multiple antigens to prevent different diseases or to protect against multiple strains of infectious agents causing the same disease. Existing combination vaccines are listed according to the year they were first licensed in the United States. Potential combination vaccines are listed in order of their number of components. Horizontal lines connect multiple antigens combined into one vaccine. Vertical alignment illustrates how antigens may be joined in different combinations.

[†]As of publication date, some vaccine combinations listed are not licensed or approved for all ages in the United States.

Adapted from: Weniger BG, Chen RT, Jacobson SH, et al. Addressing the challenges to immunization practice with an economic algorithm for vaccine selection. *Vaccine* 1998;16:1885-97.

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Abbreviations: **DT**=diphtheria and tetanus toxoids vaccine (for children); **DTaP**=diphtheria and tetanus toxoids and acellular pertussis vaccine; **DTaP-Hib**=diphtheria and tetanus toxoids and acellular pertussis and *Haemophilus influenzae* type b vaccine; **DTwP**=diphtheria and tetanus toxoids and whole-cell pertussis vaccine; **DTwP-Hib**=diphtheria and tetanus toxoids and whole-cell pertussis and *Haemophilus influenzae* type b vaccine; **HepA**=hepatitis A vaccine; **HepB**=hepatitis B vaccine; **Hib**=*Haemophilus influenzae* type b conjugate vaccine; **Hib-HepB**=*Haemophilus influenzae* type b and hepatitis B vaccine; **Hib-HepB-IPV**=*Haemophilus influenzae* type b, hepatitis B, and trivalent inactivated polio vaccine; **INF**=influenza vaccine; **IPV**=trivalent inactivated polio vaccine (killed Salk type); **Me**=measles vaccine; **Me-Mu**=measles and mumps vaccine; **Me-Rub**=measles and rubella vaccine; **MenCon**=meningococcal (*Neisseria meningitidis*) conjugate vaccine; **MenPS**=meningococcal (*Neisseria meningitidis*) polysaccharide vaccine; **MMR**=measles-mumps-rubella vaccine; **MMR-Var**=measles-mumps-rubella and varicella (chickenpox) vaccine; **Mu**=mumps vaccine; **Mu-Rub**=mumps and rubella vaccine; **OPV**=trivalent oral polio vaccine (live Sabin type); **PnuCon**=pneumococcal (*Streptococcus pneumoniae*) conjugate vaccine; **PnuPS**=pneumococcal (*Streptococcus pneumoniae*) polysaccharide vaccine; **Rv**=rotavirus vaccine; **Rub**=rubella vaccine; **Td**=tetanus and diphtheria toxoids vaccine (for adolescents and adults).

Appendix B

EVIDENCE FOR RECOMMENDATIONS*

Recommendation	Strength of evidence	Comment
Preference for Combination Vaccines	B	Parent and provider surveys
Manufacturer Interchangeability		
<i>Permissible:</i>		
Diphtheria [†] , Tetanus [†] , Hib, HepB	A	Good evidence
HepA	B	Preliminary data
<i>Discouraged:</i>		
Acellular pertussis (in DTaP, DTaP-Hib)	C	Little or no evidence
Vaccine Supply	C	
Extra Doses of Vaccine Antigens		
<i>Permissible:</i>		
HepB, Hib, MMR, OPV, Rv, Var	A	Little or no risk of adverse events for those already immune
<i>Cautioned:</i>		
Tetanus [†]	B	Frequent revaccination could cause hypersensitivity reactions

*Principal recommendations are classified by the strength and quality of evidence supporting them according to principles described elsewhere (a,b), using categories adapted from previous publications (c,d).

A=Strong epidemiologic evidence (i.e., at least one properly randomized, controlled trial) and/or substantial clinical or public health benefit.

B=Moderate epidemiologic evidence (i.e., at least one well-designed clinical trial without randomization, or cohort or case-controlled analytic studies, preferably from more than one center) and/or moderate clinical or public health benefit.

C=Epidemiologic evidence minimal or lacking; recommendation supported by the opinions of respected authorities based on clinical and field experience, descriptive studies, or reports of expert committees.

[†]Vaccines containing diphtheria toxoids and tetanus toxoids include DT, Td, DTaP, DTwP, DTaP-Hib, and DTwP-Hib. TT contains tetanus toxoid only.

Abbreviations: **DT**=diphtheria and tetanus toxoids vaccine (for children); **DTaP**=diphtheria and tetanus toxoids and acellular pertussis vaccine; **DTaP-Hib**=diphtheria and tetanus toxoids and acellular pertussis and *Haemophilus influenzae* type b vaccine; **DTwP**=diphtheria and tetanus toxoids and whole cell pertussis vaccine; **DTwP-Hib**=diphtheria and tetanus toxoids and whole cell pertussis and *Haemophilus influenzae* type b vaccine; **HepA**=hepatitis A vaccine; **HepB**=hepatitis B vaccine; **Hib**=*Haemophilus influenzae* type b conjugate vaccine; **MMR**=measles-mumps-rubella vaccine; **OPV**=trivalent oral polio vaccine (live Sabin type); **Rv**=Rotavirus vaccine. **Td**=tetanus and diphtheria toxoids vaccine (for adolescents and adults); **Var**=varicella (chickenpox) vaccine.

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