RECOMMENDED CHILDHOOD IMMUNIZATION SCHEDULE UNITED STATES—1995

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The need for a single childhood immunization schedule prompted the unification of previous vaccine recommendations made by the American Academy of Pediatrics (AAP) and the Advisory Committee on Immunization Practices (ACIP). In addition to presenting the newly recommended schedule for the administration of childhood vaccines, this article addresses the previous differences between the AAP and ACIP schedules, and provides the rationale for changing previous recommendations. (*J Natl Med Assoc.* 1995;87:537-543.)

Key words • immunization schedule
• childhood immunization

During the last 6 years, the US childhood immunization schedule has rapidly expanded to accommodate the introduction of new, universally recommended vaccines (*Haemophilus influenzae* type b [Hib] conjugate[1,2] and hepatitis B [Hep-B][2,3] vaccines), as well as recommendations for a second dose of measles-mumps-rubella (MMR)[4,5] vaccine and the use of acellular pertussis vaccines (aP).[2,6]

For many years, the Advisory Committee on Immunization Practices (ACIP) and the Committee on Infectious Diseases of the American Academy of Pediatrics (AAP)—the two expert groups that develop recommendations for vaccine use for the public (ACIP) and private (AAP) sectors—have worked together to develop similar schedules for routine childhood immunization. Some differences between the two schedules persisted, however, and the potential exists for these differences to increase as new vaccines and additional combination vaccine products are licensed for use.

The Childhood Immunization Initiative goal to deliver the primary series of childhood vaccines to at least 90% of 2-year-old children by 1996 stimulated renewed efforts for collaboration between the public and private health-care providers. In December 1993, the National Immunization Program, Centers for Disease Control and Prevention (CDC) convened a meeting of the AAP Executive Board, and representatives of the American Academy of Family Practice, the American Medical Association, and other provider groups to develop strategies for improving preschool immunization coverage. At that time, the AAP executive director mandated that the ACIP and the AAP Committee on Infectious Diseases work together to develop a unified, simplified schedule, presented in the same format by both groups. One month later, an identical mandate was issued by the Immunization Grantee Working Group, representing public providers at the state and local health department levels.

The primary reason to unify the schedule is to present clear recommendations to both private and public health practitioners and to parents. In addition, it is important to assure that the schedule defined by the ACIP for the new federally funded Vaccines for Children Program is acceptable to private practitioners. This article presents the recommended childhood immunization schedule based on vaccines licensed for use as of December 1994 and reviews the process as well as the rationale for the changes that have been made to the currently recommended AAP and ACIP schedules.

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TABLE 1. DIFFERENCES BETWEEN CURRENTLY RECOMMENDED AAP AND ACIP CHILDHOOD IMMUNIZATION SCHEDULES

Vaccine or Vaccine Dose	AAP Recommendation	ACIP Recommendation
OPV-3	6-18 months	6 months
DTP-4	15-18 months	12-18 months
Hepatitis B	0, 1-2, 6-18 months*	0, 1-2, 6-18 months†
	0-2, 4, 6-18 months‡	2, 4, 6-18 months§
MMR-2	11-12 years	4-6 years

Abbreviations: AAP = American Academy of Pediatrics, ACIP = Advisory Committee on Immunization Practices, OPV = oral poliovirus vaccine, DTP = diphtheria, tetanus, and pertussis vaccine, and MMR = measles-mumps-rubella vaccine.
*Preferred.
†Option 1.
‡Alternative.
§Option 2.

METHODS

In February 1994 a working group comprised of representatives of the AAP, the ACIP, the American Academy of Family Practice, the Food and Drug Administration (FDA), the National Institutes of Health (NIH), and the CDC was convened. Representatives from state immunization programs, the Maternal and Child Health Bureau, and vaccine manufacturers also participated. The objective was to develop a single, scientifically valid schedule, presented in a comprehensible format, that accommodated the recommendations of the ACIP and the AAP and assured the earliest timely vaccination of young children. Other immunization considerations included the number of antigens and injections to be administered at each visit, the number of visits needed during the second year of life, the availability of combined diphtheria, tetanus, and pertussis (DTP)-Hib vaccines, and the potential addition of varicella vaccine, which will likely be recommended at 12 to 18 months of age, as well as the capacity of the schedule to accommodate other newly licensed vaccines. The approach was to develop a routine schedule that identified a specific age for administering each vaccine dose, but also provided for an acceptable range of ages to ensure flexibility for the provider.

The group reviewed the differences between the AAP and ACIP schedules, as well as published studies and manufacturers' data on the immunogenicity of different schedules and simultaneous vaccine administration, particularly those data important for consideration of schedules for oral poliovirus vaccine, measles, and hepatitis B vaccines.

DIFFERENCES BETWEEN THE AAP AND ACIP SCHEDULES

The major differences between the currently recommended AAP and ACIP schedules include the timing of the third dose of oral poliovirus vaccine (OPV), the fourth dose of DTP, and the second dose of MMR as well as the schedule for infant hepatitis B vaccination (Table 1). Resolution of these differences and the scientific rationale for the decisions that were made are described in the following sections.

Effect of Age at Vaccination on Immunogenicity

Oral Poliovirus Vaccine. Since 1963, OPV has been recommended as the vaccine of choice for inducing long-lasting immunity to poliomyelitis. The primary series consisted of two doses administered during infancy at approximately 2-month intervals, a third dose recommended 6 weeks to 14 months after the second dose (generally given at 6 to 18 months of age), and a booster or reinforcing dose at 4 to 6 years of age. A study comparing two infant immunization schedules (approximately 2, 4, 6, and 12 months of age versus 2, 4, and 12 months of age) reported high seroconversion rates and similar geometric mean antibody titers after three doses with either schedule.[7] Several other studies have evaluated the seroresponse to OPV administered at 2, 4, and 6 months; 2, 4, and 12 months; and 2, 4, and 18 months of age.[8-11] These data showed excellent response to all serotypes of OPV when the third dose is given at 6, 12, or 18 months of age (Table 2).

Because response is not affected by administering the third dose of OPV as early as 6 months of age and

TABLE 2. PERCENTAGE OF CHILDREN WITH SERUM NEUTRALIZING ANTIBODY TO POLIOMYELITIS BY NUMBER OF DOSES OF OPV AND SCHEDULE

Study	Schedule	After Two Doses			After Three Doses		
		p1	p2	p3	p1	p2	p3
Hardy et al[1]	2, 4, 6 months	93	100	91	97	100	96
Cohen-Abbo et al[8]	2, 4, 6 months	89	100	93	99	100	99
Hardy et al[7]	2, 4, 12 months	92	99	90	96	100	96
Faden et al[9]	2, 4, 12 months	100	100	100	100	100	100
McBean et al[10]	2, 4, 18 months	92	100	96	97	100	100
Modlin et al[11]	2, 4, 18 months	95	100	90	95	100	100

Abbreviations: OPV = oral poliovirus.

because earlier scheduling can assure a higher rate of completion of the primary series at a younger age, 6 months of age was selected for the routine administration of OPV3, although vaccination up to 18 months remains an acceptable alternative.

Measles. *First dose.* During 1989 and 1990, when more than 55 000 reported cases of measles occurred, almost 25% were among children 15 months of age or younger (routine immunization was recommended at 15 months of age at that time). Approximately 9% of reported cases occurred in children 12 to 15 months of age (CDC. Unpublished data. 1991.). Several studies have shown that younger women with vaccine-induced immunity have lower titers of measles antibodies than women who have had natural measles infection and that the transplacental antibody acquired by their children will wane earlier, leaving these children susceptible to measles at a younger age.[12,13] This suggests that children born to younger mothers, who are likely to have vaccine-induced measles immunity, may respond well to measles vaccine administered at 12 months of age. A recent CDC study[14] in which children were randomized to receive measles vaccine at 12 or 15 months of age showed 95% measles antibody response to MMR given at 12 months of age compared with 98% response at 15 months of age. This difference was minimal in children of mothers born after 1961, who had probably received measles vaccine and are less likely to have experienced measles infection than women born in previous years.

Because a second dose of measles vaccine is routinely recommended for all children, the slightly lower response to measles vaccine at 12 months of age compared with 15 months of age will have little epidemiologic impact. In addition, earlier scheduling of the first dose of measles vaccine may improve vaccination coverage. In late 1993, both the ACIP and AAP recommended the first dose of MMR vaccine at 12 to 15 months of age.[2,15] The working group chose to retain this recommendation.

Second dose. In 1989, both the ACIP and the AAP recommended a second dose of measles vaccine; however, the ACIP recommended the second dose at 4 to 6 years of age,[5] and the AAP recommended it at 11 to 12 years.[4] Most states have implemented school entry requirements based on either or both of these recommendations. At the present time, 12 states require the second dose at kindergarten entry (4 to 6 years of age), 12 require it at middle school entry (11 to 12 years of age), and 13 states require it for both kindergarten and middle school enterers. Because response to the second dose is excellent when given to either age group (CDC. Unpublished data) and because of state-specific laws governing the administration of the second dose of MMR, the working group agreed that the second dose of MMR was acceptable at either 4 to 6 years of age or at 11 to 12 years.

Hepatitis B. Universal infant immunization with hepatitis B vaccine was recommended in 1991.[3,16] Although a protective serologic response ($\geq$10 mIU/mL) has been demonstrated among more than 95% of hepatitis B vaccine recipients who received vaccine according to a variety of schedules beginning at birth or 2 months of age (Table 3), higher antibody titers were achieved when the third dose was given at 12 or 15 months of age.[17,18] Available data indicate that higher titers of antibody will assure longer persistence of antibody[19-21]; however, the effect on long-term protection against disease is not known.

The working group agreed that the routine hepatitis B immunization series should begin at birth, with the second dose at 2 months. Acceptable age ranges for the first dose are birth to 2 months of age and for the second dose, 1 to 4 months. The third dose is recommended at 6 to 18 months. Limited available data suggest better

TABLE 3. PEAK SEROCONVERSION RATES AND GMTS FOLLOWING VACCINATION WITH HEPATITIS B VACCINE ACCORDING TO EIGHT VACCINATION SCHEDULES (BEGINNING AT BIRTH OR AT 2 MONTHS)*

Vaccination Schedule (Months)	Time After First Dose	Interval	No.	Anti-HBs % With ≥ mIU/mL	Anti-HBs GMT
First Dose—Birth					
0, 1, 2 (12)	9 months	Postdose 3	62	95	110
	13 months	Postdose 4	46	100	647
0, 1, 6	9 months	Postdose 3	78	96	262
0, 2, 4	9 months	Postdose 3	49	98	99
0, 2, 6	9 months	Postdose 3	50	98	216
First Dose—2 months					
2, 4, 6	7 months	Postdose 3	82	98	202
2, 4, 12	11 months	Postdose 3	41	100	1633
2, 4, 12	11 months	Postdose 3	52	98	1358
2, 4, 15	14 months	Postdose 3	38	97	1527
2, 4, 15	14 months	Postdose 3	50	100	3424
2, 4, 6, 15†	14 months	Postdose 4	32	100	1793

Abbreviations: GMT = geometric mean antibody titers.
*Data provided by David West, PhD, Merck Sharpe and Dohme, West Point, Pennsylvania.
†A subset of the infants vaccinated at 2, 4, and 6 months of age.

response when the third dose is given after 12 months of age (D. West, PhD, unpublished data, April 1994).

DTP and Tetanus and Diptheria Toxoids, Adult Type (Td). For many years, the approved schedule for DTP vaccine has consisted of a primary series of three doses administered at 4- to 8-week intervals and a fourth (reinforcing) dose 6 to 12 months after the third. Although customarily, the fourth dose has been given between 15 and 18 months of age, it may be administered as early as 12 months of age, provided at least 6 months have elapsed since receipt of the third dose. There are no contemporary data comparing the immunogenicity of DTP or DTaP vaccination 12 to 14 months with that at 15 to 18 months of age, either given alone or simultaneously with MMR and Hib vaccines. The working group recommended that the current schedule be continued, including the option that DTP vaccine may be given as early as 12 months of age if 6 months have elapsed since the previous dose. This permits the fourth dose to be scheduled with other vaccines given in the second year of life. DTaP currently is licensed for use only as the fourth and fifth doses of the DTP series for children 15 months of age and older,[2,6] and should only be given at these ages.

Tetanus and diphtheria toxoids adsorbed for adult use is recommended every 10 years throughout life to maintain adequate protection against tetanus and diphtheria.[6] For most persons who received a dose of DTP vaccine at 4 to 6 years of age, the first dose of Td generally is administered at 14 to 16 years of age. In a recent US serological survey of tetanus immunity,[22] the proportion of the population immune to tetanus decreased with time since last tetanus vaccination (P.J. Gergen, G.M. McQuillan, M. Kiely, T.M. Ezzati-Rice, R.W. Sutter, G. Virella, unpublished data, 1994). Among 6 to 16 year olds who had received their last tetanus immunization 6 to 10 years previously, 28% had antibody titers of <0.15 IU/mL, the optimal protective level. The working group recommended that the booster dose of Td be administered at 11 to 12 years of age (with vaccination at 14 to 16 years of age being an acceptable alternative). The earlier scheduling of this dose at 11 to 12 years of age provides a foundation for a routine preadolescent preventive care visit at age 11 to 12 years, at which time the practitioner can ensure that a second dose of measles-containing vaccine has been administered. Furthermore, it is anticipated that hepatitis B vaccination will soon be recommended for all adolescents who did not complete the series in infancy; a routine visit at 11 to 12 years of age will facilitate administration of hepatitis B vaccine and other needed vaccines to adolescents.

Simultaneous Administration of Multiple Vaccines. Simultaneous vaccination has been recommended for many years, through the use of combined products (such as DTP vaccine, trivalent OPV, and

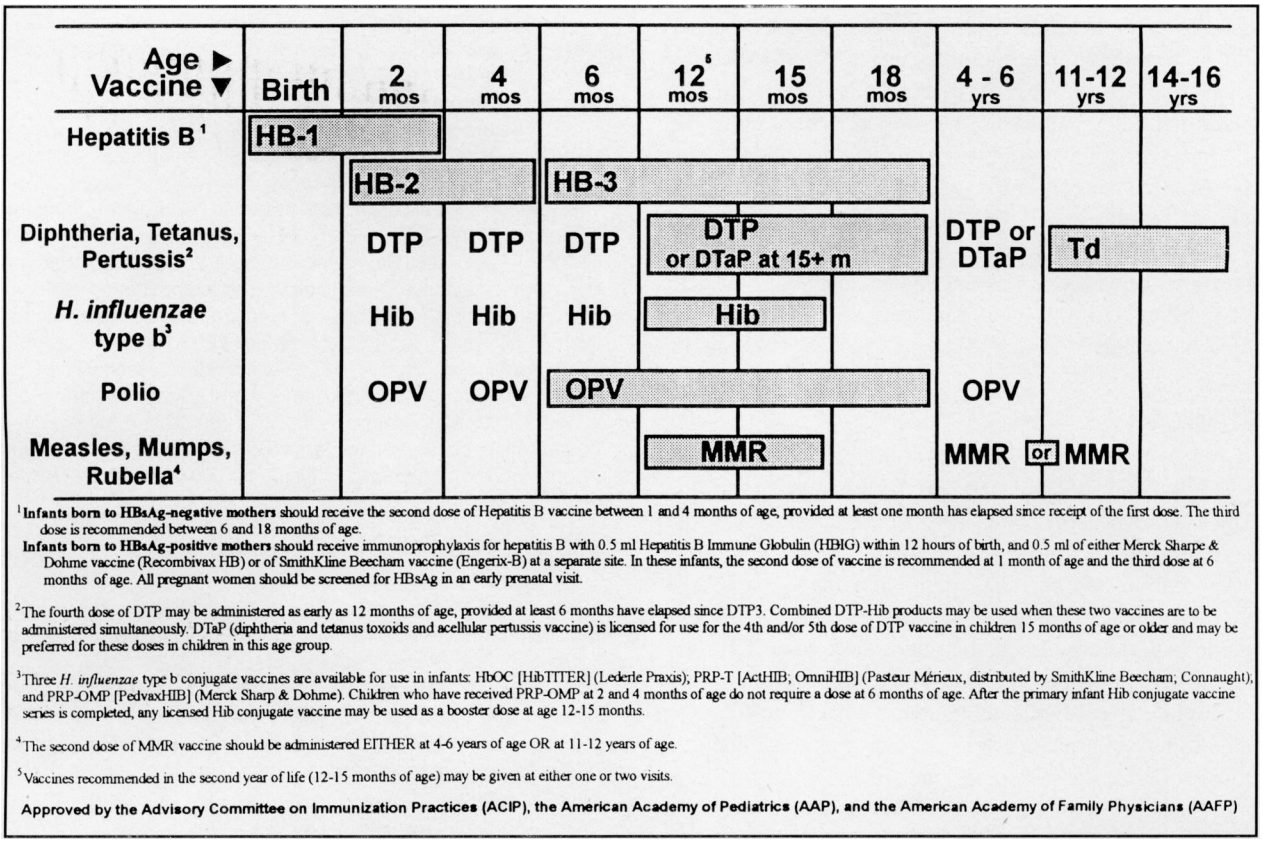

Figure. United States recommended childhood immunization schedule—January 1995. Vaccines are listed under the routinely recommended ages. Shaded bars indicate the range of acceptable ages for vaccination.

MMR vaccine) or administration of multiple vaccines at different sites or by different routes (eg, simultaneous administration of DTP, OPV, and Hib). Many studies have examined the safety and immunogenicity of simultaneously administered MMR and Hib[22,23]; DTP, OPV, and MMR[24,25]; DTP, OPV, and Hib[23,26]; and hepatitis B vaccine with DTP, OPV, or MMR (D. West, PhD, unpublished data, 1993).[27-29] Hepatitis B vaccine, the vaccine most recently licensed for infant use, has been shown to be safe and effective when administered with other routinely recommended childhood vaccines in the first or second year of life (D. Greenberg, MD, unpublished data, April 1994).[30] For a comprehensive overview of simultaneous vaccination, the reader is referred to a recently published review of the safety and immunogenicity data available for vaccines currently recommended by the ACIP and AAP during the first 2 years of life.[31]

However, there are limited data on the simultaneous administration of the entire recommended vaccine series—DTP, OPV, MMR, and Hib vaccines, with or without hepatitis B vaccine. Nevertheless, the preponderance of data demonstrating a lack of evidence of interference between routinely recommended childhood vaccines (either live, attenuated, or killed) supports the simultaneous use of all vaccines as recommended.

RECOMMENDED CHILDHOOD IMMUNIZATION SCHEDULE, UNITED STATES—JANUARY 1995

The recommended immunization schedule for children is shown in the Figure. In the first year of life, the schedule recommends three doses each of DTP, Hib, and OPV, delivered at 2, 4, and 6 months of age (although OPV3 may be administered from 6 to 18 months) and hepatitis B beginning at birth (with flexibility to start up to 2 months of age), with a second dose at 2 months of age (1 to 4 months is acceptable), and a third dose at 6 to 18 months of age.

The schedule in the second year of life is flexible, allowing practitioners to use either one visit or two

visits to deliver the vaccines recommended between 12 and 15 months of age, including DTP, Hib, MMR, and hepatitis B (if preferred). The schedule continues to recommend DTP and OPV boosters at school entry (ie, at 4 to 6 years of age) and recommends that MMR2 may be given at either entry to kindergarten or middle school. Tetanus and diphtheria toxoid is recommended at 11 to 12 years of age, but may be administered through 14 to 16 years of age. When scheduled at 11 to 12 years of age, this visit can serve to ensure that the child has received a second dose of MMR.

SUMMARY

The development of a unified childhood immunization schedule approved by the ACIP, the AAP, and the American Academy of Family Practice represents the beginning of a process that will assure continued collaboration among the recommending groups, the pharmaceutical manufacturing industry, and the FDA to maintain a common schedule and work toward further simplification of the schedule. The immunization schedule will be published semiannually, with more frequent updates as new vaccines are licensed or as recommendations for licensed vaccines are revised. In addition, ongoing studies of the efficacy of this and other schedules may result in publication at other intervals.

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