

Benefits of Combination Vaccines: Effective Vaccination on a Simplified Schedule

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Abstract

Background: The number of recommended immunizations during childhood has increased significantly over the years. Today, infants receive vaccines against 11 diseases in the first 2 years of life, and may receive as many as 5 injections at a single office visit. For a number of reasons, some injections may be deferred to a later visit, thus creating a missed opportunity for vaccination.

Objective: To review benefits of pediatric combination vaccines.

Results: Combination vaccines that protect against several diseases, such as the new DTaP-HepB-IPV (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B [Recombinant] and Inactivated Poliovirus Vaccine Combined) vaccine, can help to simplify the current immunization schedule. Other benefits of combination vaccines for parents and healthcare providers include decreased anxiety because of perceived reduction in pain for the infant, fewer missed opportunities to vaccinate, convenience, and decreased costs for the parent as a result of fewer office visits. Benefits of using combination vaccines in the office setting include reduced missed opportunities to vaccinate, storage of fewer vials, decreased risk of needle sticks as a result of handling fewer syringes, and potentially improved record keeping and tracking. Benefits of using combination vaccines in managed care include improved member satisfaction and lower costs because of fewer vaccine administration charges, and potentially fewer office visits.

Conclusions: Combination vaccines are an effective means of decreasing the number of injections and simplifying the immunization schedule, thus providing overall benefits to infants, parents, healthcare providers, office managers, and managed care administrators.

(*Am J Manag Care.* 2003;9:S6-S12)

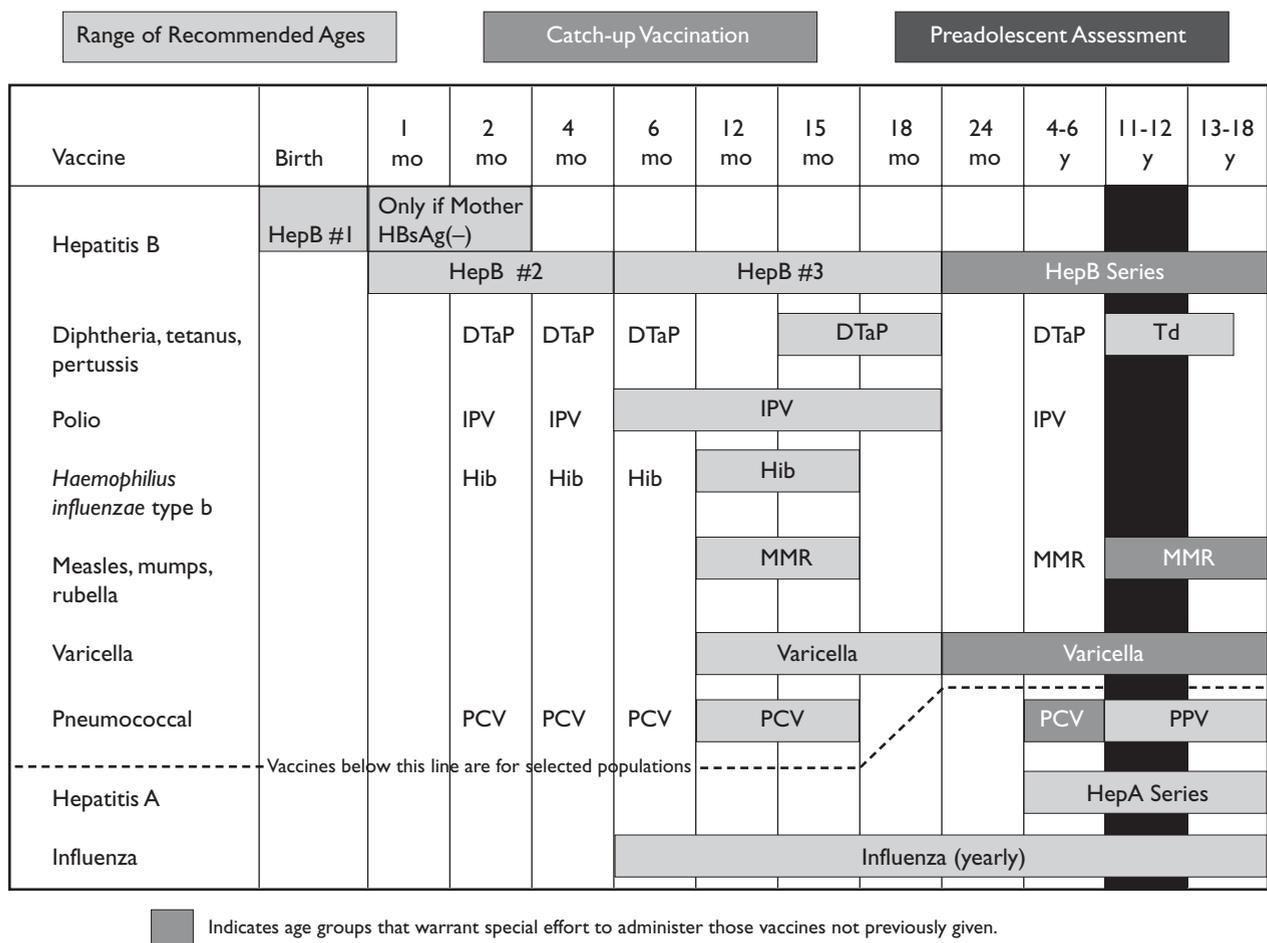
The number of vaccines recommended during childhood has increased significantly within the past few years.¹ In 1980, infants only received diphtheria-tetanus-pertussis (DTP) vaccine and measles-mumps-rubella (MMR) vaccine by injection in the first 2 years of life. Licensure of the *Haemophilus influenzae* type b (Hib) conjugate vaccines beginning in 1988 added more injections to the schedule. In 1991, the Advisory Committee on Immunization Practices (ACIP) recommended that all infants be immunized with 3 doses of hepatitis B virus vaccine (HepB) by 18 months of age.² The varicella vaccine was added to the immunization schedule in 1995 and a heptavalent pneumococcal conjugate vaccine for children younger than 5 years of age was added in 2000.³ In addition, concerns about vaccine safety led to replacement of the oral poliovirus vaccine with the injectable inactivated poliovirus vaccine (IPV). As a result, children today may receive 20 injections by the age of 2 years to complete their immunization series.¹

Simultaneous administration of vaccines is a safe and effective strategy for improving vaccination rates in children.⁴ Infants today routinely receive vaccines against 11 diseases in the first 2 years of life, and may receive up to 5 injections at one office visit to comply with the schedule for childhood immunization recommended by the American Academy of Pediatrics (AAP), the ACIP, and the American Academy of Family Physicians (AAFP)

(Figure).¹ Children whose immunizations are not up-to-date may receive as many as 7 or 8 injections during 1 office visit in order to catch up. In addition to the combination vaccines currently available, combination vaccines that contain antigens against even more diseases are needed and have been recommended to decrease the number of injections and optimize the rate of early childhood immunization.⁵ DTaP-HepB-IPV (Pediarix [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B

(Recombinant) and Inactivated Poliovirus Vaccine Combined], GlaxoSmithKline Biologicals, Rixensart, Belgium) is a new pediatric combination vaccine that can simplify the existing immunization schedule and provide protection against 5 serious childhood diseases with a primary series of 3 injections. This article will review the benefits to infants, parents, healthcare providers, office managers, and managed care administrators of using pediatric combination vaccines.

Figure. Recommended Childhood Immunization Schedule, United States, 2002



DTaP indicates diphtheria-tetanus-acellular pertussis vaccine; HBsAg, hepatitis B surface antigen; HepA, hepatitis A virus vaccine; HepB, hepatitis B virus vaccine; Hib, *Haemophilus influenzae* type b vaccine; IPV, inactivated poliovirus vaccine; MMR, measles-mumps-rubella vaccine; PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine; Td, tetanus and diphtheria toxoids. Source: Reproduced from Centers for Disease Control and Prevention.³¹

**Missed Opportunities for Vaccination:
A Growing Concern**

There is a nationwide effort to increase childhood immunization, and every encounter in the office setting needs to be used as an opportunity to vaccinate. Concerns about administering multiple vaccines at a single office visit may leave some injections to be deferred to a later visit, which creates a missed opportunity for vaccination.⁶ A missed opportunity is defined as an encounter of the patient with the provider in which there was failure to administer a required vaccine. These missed opportunities most often affect socioeconomically disadvantaged children who may not visit a physician's office regularly.⁷ Although many other factors were involved in the nationwide outbreak of measles that occurred between 1989 and 1991, more than one third of the affected cases occurred among unvaccinated individuals.^{4,8} Undervaccination also has contributed to the increase in the number of children who have acquired pertussis infection in the past 2 decades.^{9,10}

A study conducted in the Rochester, New York area evaluated specific factors that contribute to missed opportunities to vaccinate children.¹¹ Although the reasons for these missed opportunities were quite complex, the authors divided the "stumbling blocks" for adequate vaccination into 3 main categories. The first category related to patient characteristics or consumer factors. Among these characteristics were the patient's age, visit rate, insurance coverage, appointment-keeping behavior, and the presence of chronic conditions. It was noted that in inner-city practices, cumulative undervaccination rates increased as the infant approached 18 to 24 months of age. There was a greater incidence of missed opportunities for vaccination in infants covered by Medicaid or no health insurance at all, in comparison with infants covered by private insurance. In addition, there was an increased incidence of missed appointments in these infants, which further decreased the opportunities to vaccinate the child. The second category that contributed to missed opportunities included system barriers (ie, practice policies),

vaccine costs, and the lack of an adequate vaccination tracking system. The third category related to provider factors, specifically the healthcare provider's attitude and practice. More missed opportunities to vaccinate occurred during sick visits because many providers only immunize children during preventive well-child visits. Therefore, combination vaccines can help solve the problem of clinicians who refuse or are reluctant to administer multiple injections at 1 visit.

**The Future of Immunization:
Combination Vaccines**

The AAP, the ACIP, and the AAFP endorse the use of combination vaccines whenever any component of the combination is indicated and its other components are not contraindicated, provided they are approved by the US Food and Drug Administration for the child's age.^{5,12} As a result, there has been an effort to develop new combination vaccines to help simplify the immunization schedule. Many practitioners do not realize that combining multiple antigens into 1 vaccine is not a new concept—combination vaccines have been used in the United States since the 1940s.¹³ In 1945, trivalent influenza vaccine was the first combination vaccine to be licensed. Of the combination vaccines commonly used in infants today, DTP vaccine was first licensed in 1948, IPV vaccine in 1955, MMR vaccine in 1971, Hib-HepB vaccine in 1996, and the heptavalent pneumococcal conjugate vaccine was licensed in 2000.

A new combination vaccine, DTaP-HepB-IPV, provides protection against diphtheria, tetanus, pertussis, hepatitis B, and poliomyelitis when administered at 2, 4, and 6 months of age.¹⁴ The safety and immunogenicity of this new vaccine have been demonstrated through clinical trials,¹⁵⁻²⁰ and these data are reviewed by Partridge and Yeh elsewhere in this supplement. These studies have demonstrated that DTaP-HepB-IPV combined vaccine is safe and immunogenic, similar to the separate administration of its component vaccines.

Several other combination vaccines have been developed and are currently in various stages of evaluation.^{5,14,21,22} The majority of

Table. Pediatric Combination Vaccines Presently Licensed or Under Development*

Combination Vaccine [†]	Licensed in US	Licensed Outside US	Under Development [‡]
Td-IPV		AvP-Fr, AvP-Ca, AP MSD	
DT-IPV		AvP-Ca	
DT-HepB		AvP-Fr	
DTP-IPV		AvP-Ca, AvP-Fr	
DTP-Hib	AvP-US, WL	AvP-Ca, AvP-Fr, GSK, WL	
DTP-Hib-IPV		AvP-Ca, AvP-Fr, AP MSD	
DTP-HepB		GSK	
DTP-Hib-HepB		GSK	
DTaP-IPV		AvP-Ca, AP MSD, NAVA, GSK	
DTaP-Hib	AvP-US [§]	AvP-Fr, GSK	
DTaP-IPV-Hib		AvP-Ca, AP MSD, GSK	
DTaP-HepB		GSK	
DTaP-HepB-IPV	GSK	GSK	
DTaP-Hib-HepB			Yes
DTaP-Hib-IPV-HepB		AP MSD, GSK	
DTaP-Hib-IPV-HepB-HepA			Yes
HepB-Hib	Merck	AP MSD	
HepB-HepA	GSK	GSK	
MMR-V			Yes
PnC-MnC			Yes
PnC-MnC-Hib			Yes

*Products combining only multiple serotypes of a single pathogen are excluded, as are DT, DTP, DTaP, OPV, IPV, and MMR. Only manufacturers who distribute their products globally are listed; other manufacturers may produce some products (eg, DTP-IPV) for local or regional use. Some products represent components derived from, or joint efforts of, more than 1 manufacturer; in such cases, their principal distributor is shown.

[†]No discrimination is made between products distributed in combined form and those distributed in separate containers for combination at the time of use.

[‡]Indicated vaccines may be under development by more than 1 company.

[§]Licensed for the fourth (booster) dose only.

aP indicates acellular pertussis vaccine; AvP, Aventis Pasteur (Ca, Fr, US, and AP MSD designate, respectively, vaccines sourced from the Canadian, French, and US subsidiaries or the AvP-Merck European joint venture); D, diphtheria toxoid vaccine; GSK, GlaxoSmithKline; HepA, hepatitis A virus vaccine; HepB, hepatitis B virus vaccine; Hib, *Haemophilus influenzae* type b conjugate vaccine; IPV, enhanced inactivated trivalent poliovirus vaccine; MMR-V, measles, mumps, rubella, and varicella vaccine; MnC, meningococcal conjugate vaccine; MSD, Merck, Sharp & Dohme; NAVA, North American Vaccine; OPV, oral polio vaccine; P, whole-cell pertussis vaccine; PnC, pneumococcal conjugate vaccine; T, Td, tetanus toxoid vaccine; WL, Wyeth Lederle Vaccines and Pediatrics.

Source: Adapted with permission from Sewell EC et al.²³

these combination vaccines utilize DTaP as the foundation on which other vaccines such as Hib, HepB, and IPV are added (Table). However, additional combination vaccines are being evaluated,⁶ including an MMR-varicella vaccine.

Benefits of Combination Vaccines

Parents. The administration of combination vaccines is preferred by parents and healthcare providers because of the decrease in the number of injections that need to be administered at each office visit. Combination

vaccines can reduce the psychological burden brought about by the perception that the infant is in pain when receiving multiple injections.^{24,25} In a survey of family physicians, nurses, and parents, it was found that 3 injections were thought to be “too many” for a child to receive at a single office visit.²⁵ As a result, only 15% of physicians gave DTP, MMR, and Hib vaccines concomitantly to a 15-month-old infant. When universal HepB vaccination of infants was first recommended, the number of required simultaneous injections was cited as a factor as to whether physicians recommended the vaccine to parents. Therefore, the need for multiple injections may affect compliance with the recommended childhood immunization schedule.^{4,25} Conversely, advantages to administering multiple immunizations at each office visit included improved immunization rates and parental convenience and decreased costs to the parent from less frequent office visits. However, parents felt that the pain and potential adverse effects associated with multiple immunizations outweighed these benefits. Therefore, combination vaccines have the potential to offer the same benefits with fewer injections on a simplified immunization schedule.

In a study conducted by Meyerhoff et al,²⁶ in 26 geographically dispersed outpatient centers, parents expressed strong desires for limiting their children’s pain and emotional distress from simultaneous injections administered at 1 visit. A self-administered questionnaire was completed by 294 parents of infants 6 weeks to 7 months of age. This study demonstrated that parents were willing to pay significantly higher fees to reduce the pain and aggravation of multiple injections administered to their children. Although combination vaccines may cost slightly more than the total cost of their component vaccines, the benefits of administering fewer injections may outweigh the difference in cost.

It is important for healthcare providers to be informed about issues related to safety so that they are able to educate parents about combination vaccines and discuss concerns parents may have. An example of a parental concern regarding combination vaccines is the recent fear of a potential

relationship between MMR vaccine and autism.²⁷ It is important for the healthcare provider to assure parents that the vaccine does not cause autism and that separate administration of measles, mumps, and rubella vaccines provides no benefit over administration of the combination MMR vaccine.^{27,28} Emphasis must be placed on the fact that failing to administer the 3 components of the vaccine would only lead to a missed opportunity to provide adequate protection against these serious diseases.

Healthcare Providers and Office Managers. The use of combination vaccines leads to more efficiency in the office setting by decreasing shipping, handling, and vial storage needs, and thereby decreasing the likelihood of human error. Furthermore, less nursing time is needed to prepare vaccines when combination vaccines are used in the office setting.²⁹ Handling fewer syringes reduces the potential for accidental needle sticks by the office staff who are administering the vaccines.

Record keeping and immunization tracking, which are necessary for delivering the correct immunizations when they are due, also are performed by the office staff. Combination vaccines with long generic names may present a challenge for record keeping and immunization registries,³⁰ although new tracking systems, such as peel-off labels on the vaccine vial that can be applied directly to the record, may simplify these efforts.

Managed Care Administrators. There are several advantages for managed care organizations when combination vaccines are used. The first advantage relates to member satisfaction. As previously discussed, fewer injections decrease the psychological trauma of perceived infant pain for parents. Therefore, when combination vaccines are administered in managed care settings, parents will be more satisfied by the level of care.

Another advantage of combination vaccines in managed care is a reduction in costs.²¹ Various managed care organizations have set up parameters to demonstrate

proper preventive measurements to their clients. One of these is the Health Plan Employer Data and Information Set (HEDIS) score for immunizations. When immunization goals are not met, the particular provider is "penalized" (ie, they must pay a monetary fine) by the managed care organization. Therefore, combination vaccines are expected to improve HEDIS scores for immunization and decrease the financial burden on the provider. It also is anticipated that fewer injections will result in lower costs by reducing total vaccine administration charges,²³ and possibly reducing the number of office visits.

Theoretically, if combination vaccines increase immunization compliance, they may in turn decrease disease rates and reduce the need for hospitalization of severely ill children. This increase in protection for the vaccinated individual extrapolates to the community by decreasing the rate of communicable disease, thus reducing overall health-care costs. Therefore, combination vaccines may potentially impact the economy by minimizing the cost of treating vaccine-preventable diseases.

Conclusion

The routine use of vaccines has helped make our children healthier. Combination vaccines, such as the new DTaP-HepB-IPV vaccine, offer the benefit of simplifying the immunization schedule, which may lead to increased compliance, time savings for physicians and nurses in both preparation and record keeping of immunizations, and reduced administration costs. Therefore, incorporation of combination vaccines into clinical practice will benefit infants, parents, healthcare providers, office managers, and managed care administrators alike.

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