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Vaccine Update: New Policies and New Products

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The frequent changes in the recommended childhood immunization schedule make it a challenge for pediatric health care providers to keep abreast of current standards of practice. The purpose of this brief review is to provide readers with an overview of recent changes in the immunization schedule for children and the policies regarding reporting vaccine-related adverse events. In addition, new vaccine products will be briefly reviewed. For readers interested in obtaining the complete immunization schedule, the American Academy of Pediatric routinely publishes this information in the journal *Pediatrics*.[1]

The Need for Change

Immunization standards in the United States are determined by a joint effort of the Advisory Committee for Immunization Practices (ACIP), a branch of the Centers for Disease Control and Prevention, along with representatives of the American Academy of Pediatrics and the American Academy of Family Physicians. These groups not only must act to protect individual citizens (particularly children) from harm, but also concern themselves with the benefits of societal protection from disease.

Each year, a new policy statement is issued from the combined group. In the past decade, many substantial changes have been made. Several new vaccine products have been incorporated into the schedule, including *Haemophilus influenzae* type b (Hib), hepatitis B, and varicella vaccines.

Both Hib and hepatitis B vaccines have already had a significant impact on disease prevention when administered during childhood. The CDC estimates that the incidence of invasive Hib infection has declined by 95% in the United States since the release of conjugate vaccines in the late 1980's.[2] It is not unrealistic to envision the complete eradication of Hib disease within the next decade.

Likewise, hepatitis B-associated hepatocellular carcinoma may be drastically reduced by the universal immunization of children. In a report published last month in the *New England Journal of Medicine*, Taiwan demonstrated a significant decrease in pediatric cases of hepatocellular carcinoma a decade after initiating a nationwide hepatitis B vaccination program.[3]

Newer vaccine formulations with less risk of adverse effects, such as acellular pertussis products, recombinant hepatitis B, and inactivated poliovirus vaccines have also been incorporated into the recommended childhood immunization schedule.

The new recommendations also reflect a trend towards increased flexibility in timing vaccine administration, made necessary by both the increasing complexity of the immunization schedule and the need to avoid missed opportunities for vaccination in children with limited access to health care.

Adoption of the Acellular Pertussis Vaccine

One of the most recent changes in the recommended childhood immunization schedule is the addition of acellular pertussis vaccines. The original whole-cell products were associated with adverse effects in many children and less than optimal efficacy. Acellular products were developed in the 1980's in an effort to improve immunogenicity and reduce adverse events.[4,5]
The acellular pertussis products, usually given in combination with diphtheria and tetanus toxoids as DTaP, were originally studied and approved for booster shots in children 18 months of age

and older. Several large scale studies have since documented their safety and immunogenicity in younger children.[6,7] The frequency of mild to moderately severe adverse effects such as fever, irritability, and injection site reactions was substantially reduced in infants and children receiving the acellular products compared to children given whole-cell products. The rates of efficacy (disease prevention) and immunogenicity (serologic analysis) of the acellular vaccines were found to be equal or superior to whole-cell products. As a result, the Food and Drug Administration (FDA) has now approved acellular pertussis vaccines for the entire immunization series, beginning at 2 months of age.

There are currently three DTaP products available in the United States, Acel-Imune® manufactured by Lederle-Praxis, Tripedia® from Connaught, and the newly released Infanrix® made by SmithKline Beecham.[8,9]

During this period of transition, the current immunization schedule allows for the use of either whole cell (DTP) or acellular pertussis (DTaP) for the entire series, with DTaP being preferred.[1,10] It is expected that the use of whole-cell pertussis products will cease entirely within the next two to three years.

Recommendations for Polio Vaccination

For several decades, oral live-virus polio vaccine (OPV) was the standard method of immunizing children against poliovirus. The success of this vaccination program can be seen in the eradication of wild poliovirus in the western hemisphere by 1994. However, a small number of cases of poliomyelitis continue to appear in the United States each year, resulting from the use of the live-virus product. Between 1980 and 1994, 125 cases of vaccine-related polio were reported to the CDC.[11]

As a result, there has been renewed interest in the conversion to routine use of the inactivated poliovirus vaccine (IPV), which is given subcutaneously. The IPV products currently available have demonstrated equivalent efficacy to OPV. The current recommended childhood immunization schedule provides three options for vaccination: the full series with OPV, the full series with IPV, or a mixed series with IPV at two and four months. This last regimen is based on the premise that congenital immunodeficiency syndromes may not be diagnosed until several months of age. Immunocompromised children or their household contacts should only receive IPV.[1,11]

A recent survey found that most parents prefer the complete IPV series to the other options.[12] As with whole-cell pertussis, it is expected that use of the oral polio vaccine will eventually be eliminated.

Combination Vaccines

As more vaccines are added to the recommended immunization schedule, infants and children are faced with an ever increasing number of injections with each well child visit. Several vaccine manufacturers are attempting to address this issue with the introduction of new combination products.

Tetramune®, a combination of DTP and Hib, was the first combination product to become available in several decades. Since the advent of acellular pertussis vaccines, a newer product, TriHIBit®, has been released. This combination by Connaught contains their ActHIB® Hib vaccine and Tripedia® DTaP vaccine. At this time, it is approved for children 15 months and older. FDA approval in younger patients is expected within the next month.

The Hib vaccine has also been combined with hepatitis B vaccine in a product by Merck called COMVAX®. This formulation incorporates the manufacturer's Hib meningococcal protein conjugate vaccine, PedvaxHIB®, and their recombinant hepatitis B vaccine, RECOMBIVAX HB®. In a trial published in the June issue of *The Pediatric Infectious Disease Journal*, the combination was compared to the two separate vaccines. Similar rates of efficacy were found and adverse effects were limited only to inflammation at the injection site.[13]

It is important to note, however, that combination products may not always provide the same immunogenicity as the single-agent vaccines they contain. Clinical trials involving combination products are difficult to conduct and the results have been difficult to interpret.[14] Post-marketing surveillance will be important with these products in the future to truly evaluate their safety and efficacy.

Adverse Event Reporting

The criteria for reporting adverse events related to vaccine administration has also recently changed. For new practitioners unfamiliar with this system, the policies governing reporting adverse events were set by the National

Childhood Vaccine Injury Act of 1986. This regulation, which went into effect in 1988, mandates the reporting of serious adverse effects by health care providers through the Vaccine Adverse Event Reporting System (VAERS). It also created the National Vaccine Injury Compensation Program (NVICP) to provide financial compensation to affected patients and/or their families. The rationale for this policy includes both the need for accurate determination of the incidence of adverse events and protection of vaccine manufacturers from excessive liability which might affect vaccine production and availability.[15,16]

The requirements for mandatory reporting through VAERS have recently been revised to included newer vaccines.[17,18] Events that **must** be reported include:

- anaphylaxis or anaphylactic shock within 4 hours of DTP, DTaP, MMR, (either single agents or combination products) or IPV use
- encephalopathy or encephalitis within 72 hours of DTP or DTaP use
- encephalopathy, encephalitis, or a resultant seizure disorder within 5 to 15 days of MMR use
- chronic arthritis within 42 days of MMR use
- paralytic polio related to OPV use (within 30 days for immunocompetent patients, 6 months for immunodeficient patients)
- any sequela related to the above conditions

Clinicians should be aware that VAERS may be used to report <u>any</u> adverse event believed to be related to administration of a vaccine. To obtain forms or additional information, contact the program at 1-800-822-7967.[15] To file a compensation claim, contact the Vaccine Injury Compensation Program at 1-800-338-2382.[16]

The ongoing change in the United States recommended childhood immunization schedule reflects the need for expanding the scope of diseases covered, as well as reducing vaccine-related adverse events. With increased research in immunology and the availability of many new vaccine products, health care providers should continue to expect frequent changes in this aspect of pediatric care.

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Pharmacology Literature Review

<u>Cyclosporine in Transplant Patients</u>

The authors present a thorough review of the pharmacokinetics of cyclosporine in children post-transplantation. The 14 studies they evaluated are grouped by type of transplant involved. In general, children have been found to have a more rapid clearance of cyclosporine than adults. Bioavailability may also be age-related. As a result, the authors suggest adjusting dosing according to patient age and type of transplant. Cooney GF, Habucky K, Hoppu K. Cyclosporin(e) pharmacokinetics in p(a)ediatric transplant recipients. **Clin Pharmacokinet 1997;32:481-95.**

<u>Growth Hormone Review</u>

Growth hormone deficiency and the use of replacement therapy are the subjects of this extensive review. The author describes a variety

of medical conditions associated with growth hormone deficiency and provides a systematic approach to diagnosis. The table of growth hormone replacement products will be a valuable addition to the files of health care providers using this therapy. Shulman DI. Growth hormone deficiency: Current status of diagnosis and treatment. **J Pediatr Pharm Pract 1997;2:168-183.**

Isradipine in Children

Isradipine is a dihydropyridine calcium channel blocker frequently used in the treatment of hypertension in adults. At this time, isradipine is available only in an adult-strength tablet. Unlike nifedipine, however, it can be made into an oral liquid preparation for young children. This study evaluated the efficacy of isradipine in a population of 53 children with acute or chronic hypertension. The average dosage required to achieve target blood pressure values was 0.38+0.22 mg/kg/day, divided and given two or three times daily. The mean decrease in diastolic pressures after a dose was 11.8%, with a decrease of 17.4% in systolic pressures. Johnson CE, Jacobson PA, Song MH. Isradipine therapy in hypertensive pediatric patients. **Ann Pharmacother 1997;31:704-7.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 7/11/97:

1. Remifentanil (Ultiva®) a short-acting opioid analgesic, was added to the formulary. It is a pure mu-receptor agonist indicated for use in combination with other agents for general anesthesia and for maintenance of analgesia in the postoperative period. The usual dosage in patients $\geq$ 2 years of age receiving remifentanil is 0.025 to 0.2 mcg/kg/min. The dosage should be reduced in patients receiving concurrent therapy with other agents known to cause respiratory depression, such as midazolam. It has not been studied in infants. At this time, remifentanil is restricted to surgical procedures $\leq$ 30 minutes in length.

2. Mesalamine (Asacol® and Pentasa®) was added to the formulary for the treatment of inflammatory bowel disease.

3. An antiplatelet agent, anagrelide (Agrylin®), was added to the formulary for the treatment of essential thrombocythemia.

4. Aldesleukin (Interleukin-2 or Proleukin®) was added to the formulary for the treatment of renal cell carcinoma.

Editors' Note

Welcome to Our New Readers!

The staff of *Pediatric Pharmacotherapy* would like to welcome all new members of the Children's Medical Center staff. This newsletter is provided free of charge to all CMC personnel and referral physicians. If you are interested in submitting material for publication or serving on the editorial board, please contact Dr. Marcia Buck at the address listed below.

For assistance with questions related to medication use in children currently admitted to the CMC, you may contact the CMC pharmacy at 982-0920. For more in-depth consultations, you may contact Dr. Buck by phone at 982-0921 or by paging 971-6222, or one of the pediatrics pharmacy team members, Clara Jane Snipes, R.Ph. or Doug Paige, R.Ph. by paging PIC 1775. For questions concerning clinic patients, please contact Dr. Buck.

The University of Virginia Drug Information Center is also available to assist you with medication questions. Dr. Anne Hendrick is the program director. You may contact the Center by phone at 924-8034, Monday through Friday between the hours of 8:00 AM and 4:30 PM. The Drug Information Center can also provide assistance when requesting an addition to the formulary.

If you have any comments or would like to be on our mailing list, please contact Marcia Buck by mail at Box 274-11, University of Virginia Medical Center, Charlottesville, VA 22908 or by phone (804) 982-0921, fax (804) 982-1682, or e-mail to mlb3u@virginia.edu.