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Changing Carriage Rate of *Neisseria meningitidis* Among University Students

ABSTRACT & COMMENTARY

Synopsis: *Freshman college students, particularly those who live in dormitories, are at a modestly increased risk for meningococcal disease.*

Source: Neal KR, et al. Changing carriage rate of *Neisseria meningitidis* among university students during the first week of term: Cross sectional study. *BMJ* 2000;320:846-849.

Neal and colleagues note that during the 1990s there have been major increases in the incidence of invasive meningococcal disease in many developed countries, with serogroup C disease being the most common, especially among teenagers and young adults. They also note that university undergraduates have higher rates of invasive meningococcal disease than young adults of the same age who are not attending a university. This longitudinal study was performed to determine rates of carriage and acquisition of *Neisseria meningitidis*, together with risk factors for both, among university students in the absence of outbreaks.

The study was performed at Nottingham University in England. Students were recruited during their first week of attendance (October 1997). A detailed questionnaire was completed to determine medical, immunization, and travel history, as well as risk behavior during the week prior to the survey (smoking, alcohol, bar attendance, kissing, etc.). Detection of *N. meningitidis* was accomplished by culture of a posterior pharyngeal swab. A follow-up culture was obtained during either the first week of November or December 1997. During the study period, one case of serogroup C disease occurred (2 more cases occurred in the spring of 1998).

The study revealed that of the 2453 first-year students who participated, a rapid increase in carriage of *N. meningitidis* occurred during the first week (from an initial 8% to 23%). Risk factors included male sex, active and passive smoking, intimate kissing, visits to halls

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INSIDE

and nightclubs, and resident housing in coed halls. That is, factors that promote social mixing are those that also promote spread of the organism. Neal et al conclude, "Our findings support the recent introduction of meningococcal vaccination for university students."

COMMENT BY MICHAEL K. REES, MD, MPH

In 1998, the CDC in collaboration with the Council of State and Territorial Epidemiology and the Vaccine Preventable Disease Task Force initiated two studies to define the risk of meningococcal disease associated with college campuses. The results are essentially identical to this Nottingham study: freshman college students, particularly those who live in dormitories, are at a modestly increased risk for meningococcal disease.

A polysaccharide meningococcal vaccine is available in the United States for the prevention of bacterial meningitis caused by *N. meningitidis* (meningococcus) serogroups A, C, Y, and W-135. It is most effective against serogroups C and Y. It does not protect against serogroup B. Protection lasts for 3-5 years. In a press release dated Oct. 20, 1999, the Advisory Committee on Immunization Practice advised that colleges take a more active role in alerting students and parents to the potential dangers of meningococcal disease. The American College Health Association now recommends that all college students, especially freshmen living on campus, consider getting the vaccine (average cost is $65). The vaccine is routinely given to U.S. Army recruits. It should also be recommended for travelers under certain situations. For example, on April 21, the CDC reported meningitis in three New York City residents who either traveled to Saudi Arabia during the month of travel to Mecca or had close contacts who were diagnosed with the infection.

For current information on meningococcal infection and the vaccine, see the CDC website, http://www.cdc.gov/ncidod/dbmd/diseaseinfo, and the American College Health Association website, http://www.acha.org/ specialprj/men/faq.htm. (*Dr. Rees is Senior Associate in Medicine, Beth Israel Deaconess Medical Center, Instructor in Medicine, Harvard Medical School, Brookline, MA.*) ❖

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Amoxicillin/Clavulanate is More Effective than Azithromycin in Eradicating Pediatric Ear Infections

ABSTRACT & COMMENTARY

Synopsis: *Amoxicillin/clavulanate treatment for AOM results in better clinical and bacteriologic cure than azithromycin therapy.*

Source: Dagan R, et al. Bacteriologic and clinical efficacy of amoxicillin/clavulanate vs. azithromycin in acute otitis media. *Pediatr Infect Dis J* 2000;19:95-104.

This study from israeli, dominican, and u.s. medical centers examined children between 6 and 48 months of age with signs and symptoms of acute otitis media (AOM) of less than 24 hours in duration. The children were randomized in a single-blind fashion to receive either amoxicillin/clavulanate (45 mg/kg/day [amoxicillin component] in two divided doses for 10 days) or azithromycin (10 mg/kg on day 1, then 5 mg/kg once daily for 4 days). All children had tympanocentesis performed prior to the first antibiotic dose, and if positive, once again on days 4-6. Dagan and colleagues measured clinical response at 12-14 days, as well as bacteriologic cure rates.

This study included 238 children with AOM. Bacterial pathogens were identified by tympanocentesis in 71% at the start of the study. *Haemophilus influenzae* was the most common pathogen, followed by *Streptococcus pneumoniae*. Bacteriologic cure was noted in 83% of the children receiving amoxicillin/clavulanate, but only in 49% of those receiving azithromycin (P = 0.001). Clinical cure or improvement was noted in 86% of children in the amoxicillin/clavulanate group, compared to 70% of those in the azithromycin group (P = 0.023). There was no difference in overall adverse events between the groups, although amoxicillin/clavulanate had a higher rate of adverse experiences judged to be antibiotic-related (10% vs 2%, P = 0.006). Dagan et al conclude that amoxicillin/clavulanate treatment for AOM results in better clinical and bacteriologic cure than azithromycin therapy.

COMMENT BY DAVID J. KARRAS, MD, FAAEM, FACEP

While many antimicrobial agents are approved for treatment of pediatric AOM, the emergence of multiple-drug-resistant bacterial strains warrants re-examination of drug efficacy. In the case of acute pneumococcal ear infections, at least one-third of isolates are penicillin-resistant, 25% are trimethoprim-sulfamethoxazole-resistant, and at least 15% are resistant to macrolides. Drug resistance has also emerged in *H. influenzae* isolates. Because much of this resistance has been reported only in the past few years, we may not be able to rely on older studies of antibiotic effectiveness for AOM.

This is a powerful and important study. Bacteriologic cure rate is a much more stringent standard of antibiotic effectiveness than clinical cure rates alone. It should be remembered that the CDC recommends standard-dose amoxicillin for initial therapy of AOM in children at low risk for penicillin-resistant pneumococcal infections (e.g., those without multiple infections and not attending day care).[1] Amoxicillin/clavulanate is generally reserved for children at higher risk for drug-resistant infections and for treatment failures. While azithromycin is certainly more convenient to administer, it does not appear to offer other therapeutic advantages over amoxicillin or amoxicillin/clavulanate. (*Dr. Karras is Associate Professor of Medicine, Temple University School of Medicine, Director of Emergency Medicine Research, Temple University Hospital, Philadelphia, PA.*) ❖

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Pharmacology Update

Pneumococcal Conjugate Vaccine 7-Valent (Prevnar-Wyeth Laboratories)

By William T. Elliott, MD, FACP and James Chan, PharmD, PhD

The fda has approved a new pneumococcal vaccine for use in children. The 7-valent pneumococcal conjugate vaccine (diphtheria CRM_{197} protein) was given approval in February for the prevention of invasive pneumococcal disease in infants and young children. *Streptococcus pneumoniae* is a leading cause of serious illness in young children including bacteremia, meningitis, pneumonia, and upper respiratory tract infections such as otitis media. The 7-valent vaccine covers serotypes that account for approximately 80% of invasive pneumococcal disease in children younger than 6 years of age.[1] The vaccine is marketed by Wyeth-Ayerst Laboratories under the name of Prevnar.

Indications

The vaccine is indicated for active immunization of infants and toddlers against invasive disease caused by *S. pneumoniae* due to capsular serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F).

Dosage

The routine immunization schedule is 2, 4, 6, and 12 - 15 months of age. For previously unvaccinated infants 7-11 months of age, two doses should be administered at least four weeks apart and the third dose after the 1-year birthday, separated from the second dose by at least two months. For children 12-23 months of age, two doses should be administered at least two months apart. For children 24 months or older through 9 years of age, one dose should be administered. However, two doses, two months apart, should be administered to children 24-59 months in high-risk groups (e.g., sickle cell disease or anatomic or functional asplenia, HIV infected or immunocompromised, chronic illness such as nephrotic syndrome, diabetes, chronic pulmonary conditions, and symptomatic heart conditions). The dose is 0.5 mL administered intramuscularly.[2]

Potential Advantages

The conjugate vaccine is more immunogenic than the existing polysaccharide vaccine that is not effective in

children younger than 2 years of age since it is T-cell independent and does not induce immunologic memory. Vaccination of infants at 2, 4, 6, and 12-15 months with Prevnar has been shown to be efficacious in preventing invasive pneumococcal disease caused by serotypes included in the vaccine.[2,10] Efficacy based on an intent-to-treat analysis (including all children who received at least 1 dose) was 93.9% (95% CI: 79.6-98.5%) for serotypes included in the vaccine. Per protocol analysis (events occurring ≥ 14 days after the third dose) showed efficacy of 97.4% (95% CI: 82.7-99.9%). The efficacy against all serotypes was 89% (95% CI: 73.7-95.4%).[1,10] Data also suggest that the vaccine reduced acute otitis media (AOM) caused by *S. pneumoniae* and AOM-related outcomes such as visits, episodes, frequent and severe otitis, and ventilatory tube placement.[9,10]

Potential Disadvantages

Prevnar will not protect against *S. pneumoniae* disease caused by serotypes other than those included in the vaccine. It is contraindicated in patients with known hypersensitivity to diphtheria toxoid. Side effects include fever, irritability, restless sleep, vomiting, diarrhea, and injection site reactions.[2] It is not certain how or if immunization against the seven serotypes would result in emergence of less common serotypes.

Comments

Prevnar is a pneumococcal vaccine prepared by the conjugation of seven serotypes of pneumococcal polysaccharide to protein carrier reactive molecule 197 (CRM 197). CRM 197 is a nontoxic variant of diphtheria toxin isolated from cultures of *Corynebacterium diphtheriae* strain C7 (ß197). The conjugated vaccine induces T cell-dependent immune response and is therefore immunogenic in children younger than 2 years of age.[6,7] The efficacy trial involving 37,816 infants (18,906 Prevnar and 18,910 control) was conducted at Kaiser Permanente of Northern California. The control vaccine was an investigational meningococcal group C conjugate vaccine (CRM_{197}).[2,10] Efficacy was more than 93% for serotypes included in the vaccine and 89% for all pneumococcal serotypes. Black and associates also reported efficacy against visits, episodes, frequent and severe otitis, and ventilatory tube placement of 8.9%, 7.0%, 9.3%, and 20.1%, respectively, with $P < 0.04$ for all.[1] In a study conducted in Finland, Eskola and associates reported a per protocol reduction of 57% (95% CI: 44-67%) in culture-confirmed, serotype-specific AOM, a 34% (95% CI:21-45%) reduction in cultured-confirm pneumococcal (any serotype) AOM, and a 6% (95% CI: -4-16%) reduction in AOM irrespective of etiology.[9]

Clinical Implications

The previously available polysaccharide pneumococcal vaccine is not effective in children younger than 2 years of age. The development of the pneumococcal 7-valent conjugate vaccine has the potential to prevent significant *S. pneumonia*-related morbidity and mortality in children. The seven serotypes, out of about 90 known serotypes, are responsible for approximately 80% of invasive pneumococcal disease and 60% of AOM in children. The seven serotypes account for 74% of penicillin-nonsusceptible (intermediate or high-level resistance) *S. pneumoniae* (PNSP) and 100% of pneumococci with a high level of penicillin resistance.[1,4] *S. pneumoniae* is the most common cause of bacterial meningitis in children and is associated with 8% mortality as well as neurological sequelae and hearing loss.[5] The vaccine has been reported effective in preventing invasive disease, reducing AOM due to vaccine serotypes, reduction in AOM of any serotype, and reduction in AOM visits, episodes, frequent otitis, and ventilatory tube placement.[2,9,10] The preliminary recommendation of the Advisory Committee on Immunization Practices (ACIP) for Prevnar includes immunization of the birth cohort, catch-up immunization of infants up to 23 months of age, and children ages 24-59 months who are at risk for pneumococcal disease. These include children with sickle cell disease or anatomic or functional asplensia, HIV-infected or immunocompromised, chronic illness such as nephrotic syndrome, diabetes, chronic pulmonary conditions (excluding asthma), and symptomatic heart conditions. The vaccine may also be considered for children in certain ethnic groups such as American Indians, Alaskans, and African Americans.

Wyeth-Ayerst is required to submit monthly adverse event reports to the FDA for the first year. It is also committed to conduct Phase IV postmarketing studies in previously unvaccinated children receiving "catch-up" therapy for all age groups.[8] The vaccine costs $58 per dose. (*Dr. Elliott is Chair, Pharmacy Education, California Division of Kaiser Permanente, Assistant Clinical Professor of Medicine, University of California-San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.*) ❖

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A New Approach to Treatment of Filariasis: Endobacterial Targeting

ABSTRACT & COMMENTARY

Synopsis: *In a strategy termed endobacterial targeting, treatment of patients with onchocerciasis with doxycycline sterilized the nematode as a result of inhibition of its endosymbiont rickettsial organism, Wolbachia.*

Source: Hoerauf A, et al. Endosymbiotic bacteria in worms as targets for a novel chemotherapy in filariasis. *Lancet* 2000; 355:1242-1243.

Hoerauf and colleagues in germany randomized Ghanian patients with onchocerciasis to receive either no treatment or doxycycline 100 mg daily for six weeks under daily supervision. Four months post-treatment, onchocercal nodules were excised and examined in a masked fashion. When compared to the nontreatment group, administration of doxycycline was associated with a marked reduction of the number of parasites containing the endosymbiont rickettsia, *Wolbachia*. Furthermore, in all those containing *Wolbachia*, their number was also markedly reduced. And, embryogenesis in female worms was uncommon, being found in only nine of 112, compared to 65 of 106 control nematodes ($P < 0.0001$).

COMMENT BY STAN DERESINSKI, MD, FACP

Infective third-stage larvae of *Onchocerca volvulus* are transmitted by the bite of a black fly, developing into the adult stage within subcutaneous nodules of the infected host. The adults may survive for as long as 15 years and the females may produce in excess of 200 microfilariae daily; these, in turn, may each survive for up to two years, during which they migrate and may cause dermatitis, lymphadenopathy, punctate keratitis, chorioretinitis, and other ocular manifestations.

Ivermectin administration is the treatment of choice, but this drug does not effectively kill the long-living adult form of the parasite. Thus, microfilariae reappear several months after treatment with ivermectin as a result of a new cycle of reproduction in the surviving adult worms.

Wolbachia can be detected as endosymbionts in most filarial species, as well as in many arthropods, including up to 20% of insect species.[1] They are found, within vacuoles, in all developmental stages of affected filaria and are often present in large numbers in adult worms. Female nematodes are more heavily parasitized than males. In the female, the organisms are present in the reproductive tissues, suggesting vertical transmission via ova cytoplasm.

Members of the Rickettsiacea, *Wolbachia* are endosymbionts of arthropods, including up to 20% of insect species, as well as nematodes. In the latter, *Wolbachia* appear to be essential for nematode fertility. Studies of animal filariasis have demonstrated that treatment with tetracycline resulted in degeneration and sterility of adult worms.[2,3] The ability to suppress normal embryonic development during the oocyte/morula stages makes this approach of "endobacterial targeting" a potentially effective therapy that may complement or replace the use of ivermectin, a drug that largely leaves the long-living adult form intact. This treatment may also be promising in lymphatic filarial infections.

This approach may have additional benefits. Microfilariae appear to avoid eliciting a host response—until they die. Treatment, in fact, can be associated with a severe systemic inflammatory response. Fortunately, such reactions in response to successful treatment occur less frequently and less intensely after ivermectin therapy than after treatment with diethylcarbamazine, which is

no longer recommended in this infection. This systemic reaction after administration of "adulticidal" agents is seen with treatment of other filarial infections as well and has been thought to be the result of a response to the release of proinflammatory products from the dying nematode. However, recent data suggest an alternative explanation—the lipopolysaccharide of *Wolbachia* may instead be the factor eliciting this response, as well as the inflammatory response in lymph nodes.[4] It is thus theoretically possible that eliminating the *Wolbachia* and its lipopolysaccharide production may prevent the occurrence of inflammatory reactions. ❖

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Vascular Catheter Infection: A Better Prevention Strategy Than 'See One, Do One, Teach One'

ABSTRACT & COMMENTARY

Synopsis: *Institution of a standardized procedural instruction course for physicians-in-training resulted in a sustained 28% decrease in vascular catheter infection.*

Source: Sherertz RJ, et al. Education of physicians-in-training can decrease the risk for vascular catheter infection. *Ann Intern Med* 2000;132:641-648.

Despite adoption of a policy mandating maximum sterile barriers for central venous catheter (CVC) insertion, Sherertz and colleagues noted that compliance by trainees was poor. They therefore instituted a standardized one-day infection control and procedure course for third-year medical students and physicians completing their first year of training. The course included didactic instruction as well as "hands-on" training by faculty. Line insertion was taught by faculty and fellows in critical care medicine and trauma. The course was repeated one year later. In the first six-month period after the course, the rate of vascular catheter infection (primary bacteremia and local infection) in the critical care and stepdown units declined from a baseline of 4.51 per 1000 patient days to 3.53 per 1000 patient days. By the third three-month period the rate had declined further to 2.92 per 1000 patient days. The average decrease in infections was 28% ($P = 0.01$). The results were similar when expressed as infections per 1000 device days. During the same period, the number of full-size sterile drapes used per CVC insertion increased from 0.44 to 0.65 ($P < 0.001$), indicating significantly improved compliance with infection control policies. Depending on the assumptions used in the cost-benefit analysis, the net savings ranged from a low of $60,000 to a high of $800,000.

COMMENT BY ROBERT MUDER, MD

Approximately 16,000 CVC-associated bacteremias occur in ICUs in the United States annually, resulting in 500 to 4000 deaths.[1] Use of full-barrier precautions, including sterile drapes, gowns, gloves, and masks, during insertion is effective in reducing the rate of infection. Sherertz et al noted that physicians-in-training complied with these guidelines approximately 20% of the time, and instituted a formal program to try to change this behavior. The result was a significant and sustained decrease in vascular catheter infection. The effectiveness of the behavior change was demonstrated by a 50% increase in the use of full-size sterile drapes.

Although this was a pre/post-observational study rather than a randomized trial, there were no changes in policy during the study periods, and antibiotic/antiseptic impregnated catheters were not used. Sherertz et al state that there were no changes in the number of admissions or severity of illness over the study, but the actual data to confirm this are not provided.

Nevertheless, this study has several important lessons for infection control programs. The first is that a well-written policy may bear little relationship to what actually goes on in practice. It takes some degree of effort to ensure that personnel actually do things the way they're supposed to. The second is that physicians-in- training need specific instruction for invasive procedures. This instruction should be provided by senior physicians and not by residents with a year or two of additional training. In the absence of formal training, deviations from optimal practice can be passed along from one class of residents to the next ("See one done

badly, do one badly, teach others how to do one badly"). In the case of CVC insertion, standardized instruction results in improved patient outcomes and lower cost. Finally, this study adds further support to prior observations that catheter insertion and care by properly trained personnel leads to a reduction in catheter-related complications, including bacteremia,[2-4] for both peripheral and central catheters. ❖

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CME Questions

35. All of the following are true regarding amoxicillin/clavulanate for treatment of acute otitis media in children *except*:

a. It has a higher clinical cure rate than azithromycin.
b. It has a higher bacteriologic cure rate than azithromycin.
c. It is less convenient to administer than azithromycin.
d. It is first-line therapy for uncomplicated infections.

36. Which of the following is correct?

a. Ivermectin efficiently kills the adult forms of *Onchocerca volvulus*.
b. *Wolbachia* are rickettsia that produce lipopolysaccharide.
c. Onchocerciasis is transmitted by mosquito bites.
d. Diethylcarbamazine is the treatment of choice for onchocerciasis.

37. Which of the following is correct?

a. A quadrivalent meningococcal polysaccharide vaccine is available in the United States.
b. The recently approved (in the U.S.) pneumococcal conjugate vaccine contains 23 serotypes.
c. Vaccination of children with the recently approved pneumococcal conjugate vaccine should be delayed until after age 2 years.
d. The recently approved pneumococcal conjugate vaccine is contraindicated in children with sickle cell disease.

In Future Issues:

Typhoid Fever:
Vaccination Failures

UPDATES

By Carol A. Kemper, MD, FACP

Fears of West Nile Virus Displace Olympic Dressage

Source: Media site, March 23, 2000; wib@wibagency.com.

Concerns regarding the risk of West Nile Virus (WNV) infection along the East Coast have prompted officials to relocate the U.S. Olympic dressage trials from New Jersey to Florida. The trials were originally scheduled for mid-May at the U.S. equestrian team headquarters. The possible persistence of WNV identified in dormant mosquitoes that survived the winter in underground structures in New York City cinched the decision. (See, Kemper CA. *Infect Dis Alert* 2000;19:104.) In addition, horses that have been training in New Jersey may be restricted from traveling to Europe for the semi-finals, which would eliminate them from Olympic competition in Sydney in September. ■

Meningococcus W-135 in Mecca

Source: ProMED-mail post, March 26-April 28, 2000; www.promedmail.org.

Numerous countries, including the United States, England, France, the Netherlands, and Oman, are reporting an increase in cases of meningococcal infection in pilgrims returning from the Haj or in their close relatives. Many of the cases have been due to the relatively rare W-135 strain of *Neisseria meningitidis*. A total of 225 cases with 57 deaths have been reported by Saudi Arabia since the Haj in March, with at least 54 cases confirmed due to serogroup A, 50 due to serogroup W-135, and one due to serogroup B. Three cases of serogroup W-135 infection have been reported in New Yorkers, one of whom was a returning pilgrim and the other a close relative. Additional cases of W-135 infection have been reported in other countries.

Recurrent outbreaks of meningococcal infection occur each year during the Haj. This year, ~1.3 million pilgrams traveled to Mecca, all of whom are now required by the Saudi Arabian government to provide verification of vaccination against meningococcal strains A and C. Although there is evidence that some travelers may have entered the country with falsified vaccination certificates, the current vaccine requirement does not protect against W-135. Only one of two vaccines presently available in Europe provides some protection from W-135 disease. In addition, the vaccine widely used in the United States (ACYW135) may not be as immunogenic against W-135 strains as it is against A and C polysaccharides. While it may provide protection against disease, it does not prevent colonization and transmission of the organism to close contacts.

International health authorities ruefully commented that they had solved the problem of certification, but not of effective vaccination. ■

Hepatitis A & B Vaccines—What's New?

Source: *Hepatitis Control Report* Winter 1999-2000;4:7; AAP News, November 1999; www.immunize.org/news.d/aap.

You may recall that based on concerns regarding the presence of thimerosal, which contains small amounts of mercury in certain vaccines, the American Academy of Pediatrics (AAP) and the United States Public Health Service recommended in July 1999 that vaccination of infants and children with hepatitis B vaccine be delayed until children were at least 1 year of age or until a mercury-free vaccine was made available. Thimerosal has been used for many years as a preservative in vaccines (including many recombinant vaccines such as hepatitis B, diphtheria, pertussis, acellular pertussis, tetanus, and Hib), where it functions as an antimicrobial, especially in multidose containers. Concerns were raised last year that the administration of multiple sequential thimerosal-containing vaccines, especially to low-birth-weight infants, may pose a risk, although clinical evidence of mercury toxicity in vaccine recipients was lacking. The FDA gave a directive to vaccine manufacturers to replace existing vaccines with reduced mercury or mercury-free vaccines.

The FDA subsequently approved a new thimerosal-free hepatitis B vaccine (Recombivax HB Pediatric, Merck & Co., Inc.) in September. However, some physicians and hospitals may not be aware of the availability of the new vaccine and have not begun to use it—resulting in inadequate vaccination of infants. Hepatitis B vaccine can be safely reinstituted using the new vaccine for all infants. Children should be optimally vaccinated at birth or no later than 2 months of age.

The FDA has also recently approved an alternate two-dose schedule for hepatitis B vaccine in children ages 11-15. In order to improve compliance with the vaccine and limit trips to the doctor, adolescents can now receive two doses of the adult Recombivax HB (10 mcg) at 0 and 4-6 months of age in lieu of a three-dose adolescent formulation (5 mcg).

In addition, hepatitis A vaccine has been included, for the first time, in the list of recommended vaccines for children beginning at age 24 months living in certain states and counties (*MMWR Morb Mortal Wkly Rep* 1999;48:1-37). Children at risk reside in counties where the rate of hepatitis A is 20 cases or more per 100,000 population. ■