



N T I M E

Aventis Submits Application For FDA Approval of Menactra™, First Candidate Quadrivalent Conjugate Meningococcal Vaccine

Strasbourg, France – Aventis recently announced the submission of a Biologics Licensing Application (BLA) to the U.S. Food and Drug Administration (FDA) for marketing approval of the use of Menactra™ Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine for protection against meningococcal meningitis in adolescents and adults aged 11-55 years. A submission for ages 2-55 is planned for 2004 in Europe and submissions for groups below 11 years of age will follow in the U.S.

Menactra vaccine is the first quadrivalent conjugate candidate for the prevention of meningococcal meningitis, considered the most deadly form of the three main types of meningitis. This vaccine is designed to offer protection against four serogroups of meningococcal disease (A, C, Y, W-135). The regulatory submission is based on results of six pivotal studies, involving more than 7,500 clinical trial participants that received *Menactra* vaccine (also called MCV-4). The vaccine has shown an excellent safety and immunogenicity profile.

Aventis Pasteur is currently constructing a new, state-of-the-art production facility at its U.S. site in Swiftwater, Pennsylvania, to produce *Menactra* meningococcal vaccine. The new facility is intended to ensure Aventis Pasteur's ability to meet anticipated global demand for the product.

About Meningococcal disease

Meningococcal disease is a rare but devastating bacterial infection and the leading cause of bacterial meningitis, which strikes between 2,500 and 3,000 Americans – mostly children and adolescents – every year, killing up to one in five of those infected. Of survivors, up to 20% suffer long-term permanent disabilities such as hearing loss, brain damage, and limb amputations. Although the disease is most common in children under age four, in the 1990s, incidence increased substantially among 15- to 24- year-olds, and one study found a 22.5 percent fatality rate among people in this age group who contracted meningococcal disease.

About Conjugate Vaccine Technology

The current FDA-licensed meningococcal disease vaccine, Menomune® -A/C/Y/W-135 (Meningococcal Polysaccharide Vaccine, Groups A, C, Y and W-135 Combined), is made from a long chain of polysaccharides that come from the outer coat of the meningococcus bacterium, providing a limited duration of immunity. Duration of protection against meningococcal disease with Menomune A/C/Y/W-135 lasts approximately three to five years.

Menactra vaccine is a conjugate vaccine, created by attaching the meningococcal polysaccharides to a carrier protein. Historically, conjugate vaccines have been shown to induce boostable memory responses and longer-lasting immune responses than polysaccharide vaccines. Since 1990, vaccines employing conjugate technology have substantially reduced two other bacterial infections that were major causes of bacterial meningitis in young children: *Haemophilus influenzae* type b and *Streptococcus pneumoniae*.

Fact:
Conjugate vaccines boost memory response and have longer lasting immunity than polysaccharide vaccines

CT RANKS #1 IN NATION FOR IMMUNIZATION RATES

According to the most recent National Immunization Survey data, CT has the highest immunization rates in the country. Data is based on 19-35 month-old children who were born August 1999 through November 2001, who were up-to-date with their primary series of vaccinations (4 DTaP, 3 polio, 1 MMR, 3 Hep B, and 3 HiB). When varicella is added to the primary series, CT also ranked #1 at 84%. The top 5 states for highest immunization rates are as follows:

Connecticut	91.1%
Massachusetts	89.4%
Rhode Island	87.0%
New Hampshire	86.8%
North Carolina	85.6%



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2004 Childhood Immunization Schedule available

Each year, CDC's Advisory Committee on Immunization Practices (ACIP) reviews the recommended childhood and adolescent immunization schedule to ensure that it is current with changes in manufacturers' vaccine formulations and reflects revised recommendations for the use of licensed vaccines, including those newly licensed. The current schedule is effective through June, 2004. The ACIP will issue updated recommendations for influenza vaccine for children 6-23 months old beginning in Fall 2004 for the 2004-2005 flu season. The ACIP has also issued a catch-up immunization schedule for children and adolescents who start late or who are more than 1 month behind in immunization. The catch-up schedule was introduced for the first time in 2003 and remains the same in content. The 2004 schedule contains some minor changes outlined below.

- The schedule indicates a change in the recommendation for the minimum age of the last dose in the hepatitis B immunization schedule. The last dose in the vaccination series should not be administered before age 24 weeks (updating the previous recommendation to not administer the last dose prior to age 6 months);
- The range of recommended ages for the adolescent Td vaccine dose has been updated to emphasize a preference for immunizing at age 11-12 years with ages 13-18 years to serve as a catch-up interval;
- Clarification was added to the footnotes for the timing of the final vaccine doses in the series for diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine, Haemophilus influenzae type b (Hib) conjugate vaccine, and pneumococcal conjugate vaccine (PCV). The final dose in the DTaP series should be given at >4 years. The final doses in the Hib and PCV series should be given at age >12 months.
- An intranasally administered live, attenuated influenza vaccine (LAIV) is approved for use in the United States. For healthy persons age 5 to 49 years, LAIV is an acceptable alternative to the intramuscular trivalent inactivated influenza vaccine (TIV).

MMR

Merck is once again manufacturing single antigen vaccines for measles, mumps and rubella. The single vaccines must be purchased in boxes of 10 single-dose vials. Expiration is through 2005. As a reminder, state regulations for school entry require 2 doses of measles, 1 dose of mumps, and 1 dose of rubella vaccines.

Influenza *Surveillance*

In December 2003, CDC issued multiple updates on the current year's influenza activity. Surveillance data indicated that the 2003-04 influenza season began unusually early, with community activity first reported in early October. Reports of severe pediatric illnesses and deaths due to influenza created an unusually high demand for vaccine. The majority of the viruses identified have been type A (H3N2) viruses of the A/Fujian strain. Influenza seasons dominated by type A viruses typically are associated with higher levels of severe illness and death than seasons when other types of viruses predominate. Although this year's vaccine contains the Panama strain of influenza A (H3N2), it is expected to provide some cross-protection against the Fujian-like virus that are currently circulating. The other two virus strains in the vaccine influenza A (H1N1) and influenza B) closely match their circulating counterparts.

Recommendations

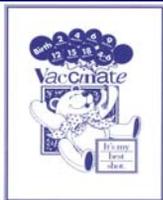
CDC recommends targeting inactivated vaccine to persons at high risk for complication from influenza. High risk groups include: healthy children ages 6-23 months, adults 65 and over, pregnant women in their 2nd or 3rd trimesters during the flu season, persons greater than two years of age with underlying chronic conditions, residents of nursing homes and other long-term care facilities, and children and teens (6 mo. -18 years of age) who are on long-term aspirin therapy and could therefore develop Reye's syndrome after influenza. Healthy persons ages 5-49 years who want to be vaccinated should be encouraged to receive live attenuated influenza vaccine if they have no contraindications.

Efficacy

The CDC routinely conducts studies to estimate the effectiveness of vaccines for the diseases they are designed to protect against. The early onset of the 2003-2004 flu season and the presence of a new, or "drifted" influenza A strain caused CDC to pursue a series of studies to answer questions about how effective this year's influenza vaccine is against the circulating viruses. The first study in the series was designed to obtain a rapid estimate of the effectiveness of the vaccine against influenza like illness while the flu season was still underway. Assessing influenza vaccine effectiveness presents unique challenges since circulating influenza viruses and influenza vaccine vary from year to year. This is the first time CDC has conducted such a study in the midst of a flu season. CDC decided to undertake this rapid study to see if it would reveal any information that would help the public, physicians and public health officials make decisions about the use of influenza vaccine, antiviral medications, or other preventive measures. Sometimes, as in this case, the studies do not yield concrete results, but do help us understand how to better approach an issue in the future.

This initial study showed that the 2003-2004 influenza vaccine was not effective or had very low effectiveness against "influenza-

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REGISTRY UPDATE

BLUE FORMS NOW AVAILABLE

Once again, pediatric practices may request the Blue School Health Assessment Forms for children going to Kindergarten in the fall. The blue forms will be returned to your practice with the child's name, DOB, and the immunizations known to CIRTS pre-printed into the appropriate boxes. Last year, 150 practices requested blue forms for 11,210 children.



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like illness" in a group of healthcare workers in Colorado. However, the study does not provide sufficient information to conclude that the vaccine is not effective at all against the dominant circulating influenza strain. For more information about influenza, visit www.cdc.gov/flu.

ACIP Statements

All clinicians should have a set of ACIP statements, the public health recommendations on vaccines, published in the *Morbidity and Mortality Weekly Report (MMWR)*. Free continuing education credits are available for reading many of the statements and completing the brief test at the end of the statement. To obtain ACIP statements:

- Download individual statements from links on IAC's website: www.immunize.org/acip
- Download individual statements from links on CDC's website: www.cdc.gov/mmwr
- Call CDC's Immunization Information Hotline: (800) 232-2522.

New (revised) Standards

In October 2003, the revised "Standards for Child and Adolescent Immunization Practices" were published in *Pediatrics*. The standards, released by the National Vaccine Advisory Committee, identify 17 strategies for effective immunization practices, including availability of vaccines, assessment of vaccination status, effective communication about vaccine benefits and risks, proper storage, administration, and documentation of vaccines, as well as implementation of strategies to improve vaccination coverage. To view the standards, including the article in *Pediatrics*, visit www.cdc.gov/nip/recs/rev-immz-stds.htm

In August 2003, the revised "Standards for Adult Immunization Practices" were published in the *American Journal of Preventive Medicine (AJPM)*.

The National Vaccine Advisory Committee led the revision effort, in collaboration with more than 60 organizations. The standards also provide links to tools and websites accessible in provider offices. To view the standards, including the article in *AJPM*, visit www.cdc.gov/nip/recs/rev-immz-stds.htm

Pneumococcal Conjugate Vaccine

On February 13, 2004, CDC recommended that health care providers temporarily suspend routine use of the fourth dose of 7-valent pneumococcal conjugate vaccine (PCV7) when immunizing healthy children. This action was taken to minimize the likelihood of shortages until Wyeth Vaccines is able to restore production capacity. Since that recommendation was issued, PCV7 production has been much less than had been expected and shipments have been delayed resulting in shortages of vaccine. Widespread shortages may continue beyond this summer. To further conserve vaccine, CDC, in consultation with the American Academy of Pediatrics, the American Academy of Family Physicians, and the Advisory Committee on Immunization Practices, recommends that all health care providers temporarily suspend routine use of both the third and fourth doses, effective immediately. It is critical that all providers immediately follow this recommendation, regardless of their current vaccine supply. Children at increased risk of severe disease should continue to receive the routine, 4-dose series. On March 5, 2004, CDC published an MMWR article describing in this revised recommendation. This recommendation reflects CDC's assessment of the existing national PCV7 supply and may be changed if the supply changes. Updated information about the national PCV7 supply is available at www.cdc.gov/nip/news/shortages/default.htm

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INVALID SHOTS HURT THE MOST

According to a recent study published in the American Journal of Preventive Medicine, (see Evaluation of Invalid Doses, Am J Prev Med 2004;26(1)) invalid vaccine doses have a negative impact on parents, physicians, and vaccine purchasers.

The study found that in an analysis of a national survey conducted in 2000 of children aged 19 to 35 months, 594,822 (11%) received at least one invalid dose of vaccine. Over half of the invalid doses were from the hepatitis B series, the vaccine with the most complicated schedule.

Similar assessments done at the state level using registry data indicate parallel findings of invalid doses. Most commonly found invalid doses include:

- ⊕ Hep B #3 not given on or after 6 months of age
- ⊕ DTaP #4 given less than 6 months after the 3rd dose
- ⊕ MMR not given on or after 12 months of age
- ⊕ Varicella not given on or after 12 months of age
- ⊕ HiB not given on or after 12 months of age
- ⊕ Polio #1 given before 6 weeks of age

Reasons for invalid doses

Receiving vaccines from more than one provider

Basing immunization decisions on incomplete information could easily lead a provider to unknowingly administer a vaccine at an inappropriate interval. Therefore it is essential that providers make every effort to obtain complete immunization histories from patients who may have been vaccinated elsewhere.

Foreign-born children

According to the study, foreign-born children were found to be 3.4 times more likely to receive an invalid dose, compared to children born in the US. Vaccination requirements and schedules in other countries are slightly different than the requirements used in the US.

Adherence to schedule

The standards for Pediatric Immunization Practice recommend that providers utilize all clinical encounters to screen for needed vaccines and, when indicated, immunize children. By doing this, providers can reduce the number of missed opportunities to vaccinate. However *some providers may do this at the expense of proper timing and spacing of immunizations.* Site visits conducted by state immunization program staff and its contractors are an opportunity to educate physicians and their staff about the immunization schedule and proper timing of vaccines, the frequency of invalid doses and the potential consequences.

DEPARTMENT OF PUBLIC HEALTH IMMUNIZATION PROGRAM MORBIDITY REPORT

Disease	Total Cases 2002	Total Cases 2003
Measles	0	0
Mumps	1	1
Rubella	0	0
Congenital Rubella Syndrome	0	0
Diphtheria	0	0
Tetanus	0	0
Pertussis	30	73
Hib	0	0
Varicella	1,816	1,562

Cost Implications

The cost of repeating doses could be quite large. In the aforementioned survey, if the 594,822 children identified in the study repeated at least one invalid vaccine, the vaccine purchase cost alone could range from \$10 million (if all vaccines were purchased at the federal contract discount prices) to \$19 million (if all vaccines were privately purchased).

Immunization Coverage Implications

When looking at the most frequently cited invalid dose (Hep B # 3), immunization coverage levels saw a significant drop (over 6%) in the overall immunization rate when the invalid dose was not counted.

The study concluded that computerized systems would likely prevent children from receiving invalid doses of vaccine. Immunization registries can inform providers of the earliest day a child should receive a given immunization, as well as identify previous vaccines administered too early. Finally, efforts for vaccinating U.S. children should emphasize that vaccines must be delivered at intervals consistent with guidelines in order to maximize immunogenicity and minimize risk of vaccine-preventable illness.

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