Questions and Answers from the November 22, 2004 Audio Conference 2004-2005 Guidelines: Influenza Vaccine/Antivirals for Persons Living with HIV/AIDS

1. What is the government doing to prevent this shortage of influenza vaccine in the future?

We (the Centers for Disease Control and Prevention [CDC], the Food and Drug Administration [FDA], and the Department of Health and Human Services [HHS]) are working with the influenza vaccine companies in several ways. Aventis Pasteur believes it has the capability to produce the same or more doses of influenza vaccine for the 2005–2006 influenza season. In addition, MedImmune has indicated that it has the capability to produce 10 million doses of FluMist for the 2005–2006 influenza season and as many as 40 million doses by 2007. We will continue to work with Chiron Corporation, in close collaboration with the UK regulatory authorities, to help Chiron address, as quickly as possible, the manufacturing problems they experienced this year. In addition, FDA has been encouraging foreign licensed manufacturers to apply for US licensure and is providing clear pathways to efficiently reach this goal.

In each of its past 2 budget requests, HHS has asked for $100 million to shift vaccine development to new cell-culture technologies and to provide year-round availability of eggs for egg-based vaccine. We received $50 million in the FY04 budget for this activity and urge Congress to fully fund the $100 million request in the FY05 budget.

Under the Current Good Manufacturing Practices (cGMP) initiative, FDA is working with industry to encourage the use of advanced technologies as well as quality systems and risk-based approaches that build quality into the manufacturing process. FDA is also using the same quality systems and risk-based approaches to modernize our regulatory responsibilities with regard to manufacturing. For example, we are providing advanced training for manufacturing investigators.

FDA is taking an inventory of foreign manufacturing of US-licensed products that are critical to public health, such as influenza vaccine, and will put into place, as needed, information-sharing agreements with other national regulatory authorities. In addition, we recognize that public health needs and resources are increasingly global in nature; in the hope that vaccines can be licensed in multiple regions of the world, FDA has been encouraging more internationally harmonized product development.

We will also address in various populations the effectiveness of reduced doses of influenza vaccine, such as intradermal vaccination or using half the current dose intramuscularly. We will evaluate whether any of these approaches for increasing the available vaccine supply could be used in the near future.

2. What about the study in Japan, where 18% of the children experienced resistance to antiviral med?

A recently published study reported an 18% frequency of neuraminidase-inhibitor resistance for a small group of Japanese children treated with oseltamivir. This is higher than the 5.5% resistance reported from a larger outpatient pediatric oseltamivir treatment study in the United States (N=182). It should be noted that the Japanese study detected resistance to neuraminidase inhibitors in young children (including outpatient and hospitalized children), the dosage of oseltamivir used for young children in Japan is lower than that used in the United States, the study was smaller (N=50) than the US study, and the molecular methods used to determine neuraminidase-inhibitor resistance were different than the standard assays that are used worldwide. Nevertheless, this study in Japan has implications for use of oseltamivir, and continued surveillance for neuraminidase-inhibitor resistance is warranted.

3. What about the shortage of antivirals in California (Strategic National Stockpile)?

Only state health departments are eligible to request antiviral medications from the Strategic National Stockpile (SNS). The SNS will review each request; and after determining that sufficient attempts have been made to acquire antiviral medications from distributors and manufacturers, it may release influenza antiviral medications to the state. The state health department will determine how the medications should be distributed. In general, they will only be for use in outbreak settings, such as an outbreak in an institution, and the manner of treatment and chemoprophylaxis will be at the discretion of the clinicians involved in the outbreak. CDC guidelines for this are at http://www.cdc.gov/flu/professionals/treatment/0405antiviralguide.htm.

4. Won't HIV+ children with low CD4 counts have low response to influenza vaccine?

Limited information is available regarding the frequency and severity of influenza illness or the benefits of influenza vaccination for persons with HIV infection. Several reports indicate that influenza symptoms might be prolonged and that the risk for complications from influenza increases for certain HIV-infected persons. Influenza vaccination has been shown to produce substantial antibody titers against influenza in vaccinated HIV-infected persons who have minimal AIDS-related symptoms and high $CD4^+$ T-lymphocyte cell counts. A limited randomized, placebo-controlled trial showed that influenza vaccine was highly effective in preventing symptomatic, laboratory-confirmed influenza infection among HIV-infected persons who had a mean of 400 $CD4^+$ T-lymphocyte cells/mm^3; a limited number of persons who had $CD4^+$ T-lymphocyte cell counts under 200 were included in that study. A nonrandomized study among HIV-infected persons determined that influenza vaccination was most effective for persons with more than 100 $CD4^+$ cells

and for those with fewer than 30,000 viral copies of HIV type-1/mL. For persons who have advanced HIV disease and low $CD4^+$ T-lymphocyte cell counts, influenza vaccine might not induce protective antibody titers; for these persons, a second dose of vaccine does not improve the immune response. Because influenza can result in serious illness and because influenza vaccination can result in the production of protective antibody titers, vaccination will benefit and is recommended for HIV-infected persons, including HIV-infected pregnant women, regardless of their $CD4^+$ cell count. For more information, please see the Advisory Committee on Immunization Practices recommendations for influenza vaccination at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5306a1.htm.

5. Can influenza antiviral medications be obtained through the ADAPT formulary program?

The AIDS Drug Assistance Program (ADAP) provides medications for the treatment of HIV disease and provides services that enhance access and adherence to and monitoring of drug treatments. The program is funded through Title II of the Ryan White Care Act, which provides grants to states and territories. The ADAP in each state and territory decides which medications will be included in its formulary and how those medications will be distributed. At least one state has made antiviral medications available in its formulary on an emergency and temporary basis for this influenza season. For more information on ADAP, see http://hab.hrsa.gov/programs/factsheets/adap1.htm.

6. What is a source of information about the avian influenza pandemic?

Current information about human infections with avian influenza A (H5N1) viruses are available on the CDC Web pages: http://www.cdc.gov/flu/avian/index.htm and the World Health Organization Web pages: http://www.who.int/csr/don/archive/disease/influenza/en/.

Information about poultry H5N1 outbreaks are available on the Office International des Epizooties (OIE) Web site: http://www.oie.int/eng/en_index.htm.

Further information about avian influenza among poultry in Asia is available on the Food and Agriculture Organization of the United Nations (FAO) Animal Production and Health Division Web site: http://www.fao.org/ag/againfo/subjects/en/health/diseases-cards/special_avian.html.

7. What data are available on effectiveness of influenza mist with HIV+ persons?

There are at least 2 published studies on this topic; they address safety and immune response but not vaccine effectiveness directly. King et al (J Infect Dis. 2000 Feb;181(2):725–8) studied 57 adults who were HIV infected (CDC class A1-2) and 54

adults who were not HIV-infected. Participants, who were not prescreened for influenza susceptibility, were randomly assigned to receive trivalent live attenuated influenza vaccine (LAIV) or placebo intranasally. LAIV was safe and well tolerated with no serious adverse events attributable to the vaccine. Rates of reactogenicity were similar for LAIV and placebo recipients except that runny nose/nasal congestion was significantly more common in LAIV recipients regardless of HIV status. No prolonged shedding of LAIV was observed in HIV-infected recipients. HIV RNA levels were not increased and CD4 counts were not decreased after immunization in HIV-infected LAIV recipients compared with placebo recipients. Shedding of LAIV and increases in antibody titers were infrequent, consistent with prior experience in unscreened adults. The data suggest that inadvertent vaccination with LAIV in relatively asymptomatic HIV-infected adults would not be associated with frequent significant adverse events.

This same group later reported on a similar, small study of children (Pediatr Infect Dis J. 2001 Dec;20(12):1124–31). They assessed the safety of LAIV administered to relatively asymptomatic or mildly symptomatic HIV-infected children and to children not infected with HIV. They found no significant differences in rates of reactogenicity events and vaccine-related adverse events after receipt of the first dose of LAIV or placebo within each HIV status group; they also found no differences after each dose of LAIV between children who were HIV infected and not HIV infected. Overall, none of the HIV-infected children experienced a significant LAIV-related serious adverse event or influenza-like illness, making the one-sided 95% confidence interval (CI) of such a serious event occurring after LAIV 0% to 12%. No significant changes in geometric mean HIV RNA concentrations, CD4 counts, or CD4% or prolonged or increased quantity of LAIV virus shedding occurred in HIV-infected children after receiving either dose of LAIV. All recovered influenza isolates retained the temperature-sensitive phenotype. After 2 doses of LAIV, 83% of the children who were not HIV infected and 77% of the children who were HIV infected had a 4-fold or greater rise in influenza antibody to at least 1 of the 3 LAIV strains.

8. What is being done to make vaccine more readily available?

On October 5, 2004, CDC and the Advisory Committee on Immunization Practices (ACIP) issued interim influenza vaccine recommendations that targeted 8 priority groups for vaccination with this year's limited supply of vaccine. These groups included persons aged 2 to 64 years who had chronic medical conditions (including persons with HIV/AIDS). CDC has worked with Aventis Pasteur, the remaining supplier of inactivated influenza vaccine, to allocate remaining vaccine to providers and organizations that serve priority patients. Most recently, CDC is working with state health departments on apportioning influenza vaccine to them. The state health departments will in turn allocate vaccine to providers and organizations best able to vaccinate priority patients.

CDC, FDA, and HHS are also evaluating whether inactivated influenza vaccine licensed in other countries could be purchased and used in the United States under an

Investigational New Drug (IND) protocol. As many as 5 million doses of vaccine may be available from these manufacturers; however, even if this vaccine is approved for an IND, we would not expect delivery of most of this vaccine until December 2004 and January 2005.

9. What is the priority for administration on the basis of T-cell counts?

CDC and ACIP have not recommended subprioritizing persons within or across the priority groups mentioned in the interim influenza vaccine recommendations. For persons with HIV/AIDS, those with severe immunosuppression may not mount an adequate antibody response. However, CD4 counts are not clearly predictive of response or nonresponse to vaccination. Therefore, ideally all persons with HIV/AIDS should receive inactivated influenza vaccine. Persons with advanced HIV disease may have a poor response to immunization. Therefore, chemoprophylaxis (use of antiviral medications for prevention) should be considered for these patients if they are likely to be exposed to people with influenza. (CDC has developed interim recommendations for the use of antiviral medications during the 2004–2005 influenza season, available at http://www.cdc.gov/flu/professionals/treatment/0405antiviralguide.htm).

10. Is the use of pneumonia vaccine part of the formal recommendations?

Pneumococcal disease, caused by *Streptococcus pneumoniae*, is a common cause of bloodborne infection, meningitis, and pneumonia; it commonly causes infection after influenza virus infections.

There are 2 vaccines for preventing pneumococcal infections. One, called Prevnar and manufactured by Wyeth Vaccines, is for children. Prevnar is a 7-valent (containing antigens from 7 serotypes of *S. pneumoniae* bacteria) pneumococcal conjugate,vaccine. The other, called Pneumovax and manufactured by Merck, is a 23-valent vaccine for older children (older than 2 years) and adults. Neither vaccine is a substitute for influenza vaccine, but each can help prevent some common complications of influenza.

Prevnar, the pneumococcal conjugate vaccine, is recommended for all children younger than 2 years and for children 2 to 4 years of age who have certain chronic illnesses or any immunocompromising condition. Clinicians should consider giving the vaccine to all children aged 2 to 4 years, especially those who are 24 to 35 months of age, African American or Native American, or attending group daycare.

The conjugate vaccine prevents bacteremia, pneumonia, and otitis media caused by pneumococci that are one of the vaccine serotypes. It also reduces carriage and transmission of vaccine-type pneumococci. Use of the vaccine in children has been shown to reduce cases of invasive disease in adults.

ACIP recommends that all adults aged 65 and older and those aged 2 to 64 years who have an immunocompromising condition, including HIV/AIDS, or certain underlying medical conditions be vaccinated against pneumococcal disease with pneumococcal polysaccharide vaccine. These persons include most of the same persons in the CDC priority groups for influenza vaccine during this season of influenza vaccine shortage.

Prevnar is now in adequate supply. Given recent and prolonged shortages, many children may not be adequately immunized. Parents and providers should make sure that children are fully vaccinated. Although the full schedule recommended for infants is 4 doses, a recent National Immunization Survey indicated that about 86% of children aged 19 to 35 months had received 1 or more doses, but only 67% had received 3 or 4 doses.

A detailed list of the conditions that are indications and a concise table of the vaccine schedule can be found at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5336a8.htm.

Merck, the sole manufacturer of pneumococcal polysaccharide vaccine, indicates that it currently has adequate supplies on hand and is tripling normal production volumes to meet anticipated increase in demand.