THE CSTE WASHINGTON REPORT

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INSIDE THIS ISSUE

EDITOR'S NOTE:. An international team of scientists, including researchers from the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, report using antibodies derived from immune cells from recent human survivors of H5N1 avian influenza to successfully treat H5N1-infected mice as well as protect them from an otherwise lethal dose of the virus."The possibility of an influenza pandemic, whether sparked by H5N1 or another influenza virus to which humans have no natural immunity, is of serious concern to the global health community," says NIAID Director Anthony S. Fauci, M.D. "If the success of this initial study is confirmed through further laboratory and clinical trials, human monoclonal antibodies could prove to be valuable therapeutic and prophylactic public health interventions for pandemic influenza"-- additional details are provided in this *Washington Report*.

The *CSTE Washington Report* is provided as an information resource for members of the Council of State and Territorial Epidemiologists on federal legislation and regulation affecting public health and epidemiology in the U.S. Legislation cited in the report can be accessed via http://www.thomas.loc.gov Regulations cited can be accessed via http://www.gpo.gov

LABOR-HHS-EDUCATION APPROPRIATIONS SUBCOMMITTEE GETS $6.6 BILLION ALLOCATION INCREASE – Yesterday, June 5th, the House Appropriations Committee made its 302(b) allocations to its 12 Subcommittees. The Labor, Health and Human Services and Education Subcommittee which funds all of CDC programs, received a $6.6 billion increase over FY 2007 and more than $10 billion over the President's budget request. The Subcommittee is scheduled to mark up its bill tomorrow, June 7th. Full Committee action is scheduled for June 14th and floor action the week of June 18th. A major concern for public health advocates is a promised veto by the White House of any appropriations bill that exceeds the President's budget request. The conservative Republican Study Group is circulating a sign on letter to Republican Members committing signers to vote to uphold any such veto. The letter currently has 138 signers, including 13 appropriators. A total of 146 is needed to uphold a veto. Health and education groups will meet on June 11th to develop strategy to protect the Labor-HHS-Ed bill by attracting enough votes on the House floor to ensure a later veto override.

RECENTLY INTRODUCED LEGISLATION OF INTEREST – On May 9th, Sen. Tom Harkin (D-IA) re-introduced the HeLP America Act, or Healthy Lifestyles America Act (S. 1342) which was first introduced in the 109th Congress. This is a comprehensive bill designed to improve the health of Americans and reduce health care costs by reorienting the Nation's health care system toward prevention, wellness, and self care. It has no co-sponsors or companion measure and has been referred to the Committee on Finance.

Also on May 9th, Sen. Hillary Rodham Clinton (D-NY) introduced the Diabetes Treatment and Prevention Act (S. 1415), a bipartisan bill. The bill, which has been referred to the Health, Education, Labor and Pensions Committee, directs the CDC Director to establish a Division of Diabetes Translation to eliminate the preventable burden of diabetes. In FY 2008, $90 million is authorized to the new Division to carry out the following activities:

(1) Supporting and carrying out diabetes surveillance.
(2) Conducting applied translational research, including research that will improve early detection, prevention, and access to quality care with respect to diabetes.
(3) Working with States to establish and improve diabetes control and prevention programs.
(4) Coordinating the National Diabetes Education Program in conjunction with the National Institutes of Health.
(5) Increasing education and awareness of diabetes.
(6) Promoting greater awareness of the health effects of uncontrolled diabetes.
(7) Other activities as deemed appropriate by the Director.

On May 16th, Sen. Tom Harkin (D-IA) introduced a bipartisan bill to improve screening and treatment of cancers and provide for survivorship services (S. 1415). The bill would provide funding through the CDC for up to five state demonstration projects to implement cancer screening programs for any such screening which receives a A or B

rating by the Preventive Services Task Force. The program would operate like the current breast and cervical cancer screening program, focusing on low income individuals and providing states with the option to cover treatment of cancers found through screening under Medicaid. The bill has been referred to the Committee on Finance.

CDC MEDIA UPDATE: XDR TB PUBLIC HEALTH INVESTIGATION -- The Centers for Disease Control and Prevention provides the following update regarding its investigation and public health actions related to a patient with extensively drug-resistant tuberculosis (XDR TB). CDC is recommending that passengers and crew on two trans-Atlantic flights taken by the patient be notified of potential exposure to tuberculosis and evaluated for TB. On May 12, the patient flew from Atlanta, Georgia, to Paris, Francis on Air France flight #385/Delta Airlines flight #8517. On May 24, the patient flew from Prague, Czech Republic, to Montreal, Canada, on Czech Air flight #0104. There were 292 U.S. residents or citizens on the Air France/Delta flight and two on the Czech Air Flight (the patient and his wife).

Update: Notification of Passengers

As of 12 p.m. on June 2, 2007, there were 292 U.S. residents or citizens identified as having traveled on the Air France flight. Earlier reports identified 310 U.S. citizens or residents on the flight, but that number was updated to 292 based on elimination of duplicate names.

As of 3 p.m. on Saturday, June 2, 2007, CDC staff has talked directly with 160 of the 292 U.S. residents or citizens on board the Air France/Delta flight (i.e., 55 percent), and are actively pursuing contact with the other 132. The 160 contacts range from talking directly to passengers, family members, or relatives (in some cases the U.S. passengers are living in or still visiting other countries). All 26 U.S. passengers in five highest priority rows (i.e. the row the passenger was in and the two rows in front and behind) have been contacted. Six of those are currently outside of the United States and family members or relatives were contacted.

Update: Denver Health Authority Public Health Department Issues Isolation Order

The Denver Health Authority Public Health Department has issued an order that requires that the patient be detained at National Jewish Medical and Research Center until further laboratory tests indicate that he is no longer contagious. The patient is currently considered infectious based on three respiratory tract specimens that were reported culture positive for extensively drug-resistant tuberculosis (XDRTB).

Since the order by local public health authorities puts in place measures that are sufficient to protect the public's health, the federal isolation order that has been used to ensure the patient remains in medical isolation is no longer in place. CDC will continue to provide input and consultation to appropriate authorities on the diagnosis, management and methods for preventing the spread of communicable disease.

Update: CDC activities

CDC will be undertaking a number of reviews related to this XDR TB case. One aspect of this review will be looking at how the CDC employee who is related (father-in-law) to the patient was involved in this matter.

Information for Media Audiences

Many recent media stories have conveyed information or impressions regarding tuberculosis that are inaccurate, including information about how the disease is transmitted, how quickly people may become infected or show symptoms, and the contagiousness of the disease.

There are some other important characteristics of tuberculosis that need to be conveyed:

Only a person with active TB disease can spread TB bacteria to others.

• Persons who have spent prolonged time with someone with active TB disease should get tested for TB infection. It usually takes prolonged exposure to someone with active TB disease for someone to become infected.

• After exposure, it usually takes 8 to 10 weeks before the TB test would show if someone had become infected.

• A person with a positive test for TB infection (i.e., latent TB infection) is not sick, and cannot spread TB germs to others. However, some of these persons can go on to develop TB disease, especially if their immune system is weak, for example, HIVinfected persons, persons with diabetes, or persons undergoing treatment for certain forms of cancer.

Frequently asked question: What should a person do if they were on the Air France flight #385 / Delta flight 8517 on May 12 with the XDR TB patient?

They need to go to their doctor or local health department and request a TB evaluation, as well as contact their State TB Control Office. They should be evaluated for signs and symptoms of TB disease, and get a TB skin test or the QuantiFERON®TB Gold blood test (QFT-G) to test for TB infection.

It can take 8 to 10 weeks after infection for a person's immune system to react to the TB skin test or QFT-G. It is important to get a TB test as soon as possible because people may already have latent TB infection, but are unaware since there are no signs and symptoms. The first test is needed to determine whether a person already had latent TB infection before this recent exposure. A person with latent TB is not infectious.

If a person's first test is negative, they will still need to get a second TB test 8 to 10 weeks following the flight date (i.e., the time of their last possible exposure to the patient) to determine if they may have been infected by the XDR TB patient. If the first

test is positive, their doctor or nurse may do other tests to see if treatment is needed.

For additional information call 1- 800-CDC-INFO (1-800-232-4636).

For more information about XDR TB, please visit http://www.cdc.gov/tb/xdrtb/.

BLOOD TEST MAY HELP SIGNAL TUMOR'S REMISSION, RETURN IN THROAT CANCER PATIENTS -- A blood test that detects proteins commonly released by a growing tumor could one day become a useful tool for monitoring the effectiveness of chemotherapy and radiation treatment in people with advanced throat cancer, according to a study published in the June 1, 2007, issue of *Clinical Cancer Research*. Scientists in the National Institute on Deafness and Other Communication Disorders (NIDCD) and National Cancer Institute (NCI), two of the National Institutes of Health (NIH), in collaboration with researchers of the University of Michigan, found that throat cancer patients who showed a decline in several cancer-related proteins following chemotherapy and radiation treatment were more likely to remain in remission, while those who experienced a large rise over time in those proteins frequently exhibited a return of throat cancer. The findings could help lead to the development of a blood test that enables doctors to detect the recurrence of throat cancer early on, when there is still time to pursue a second line of treatment, such as surgery or drug therapy.

"Cancers of the head and neck are insidious because surgical removal of the tumor can severely impair a person's ability to talk and to swallow," said NIDCD Director, James F. Battey, Jr., M.D., Ph.D. "A blood test that enables doctors to closely monitor a patient's rehabilitation while sparing the patient's voice, speech, and swallowing ability is an excellent example of the predictive, preemptive, and personalized approach to medicine that the NIH strives for."

Roughly 20 years ago, the primary method for treating throat cancer was to surgically remove the tumor. Because this treatment can severely impair a patient's quality of life by damaging voice, speech, and swallowing, in many cases physicians and their patients are now opting for a combination of chemotherapy and radiation as a first line of treatment. However, there is no way to predict which patients will respond well to this treatment or whether a tumor will return later. Clinical exams, X-rays, and magnetic resonance imaging (MRI) are currently used to monitor a patient's progress, but observation by these methods has been difficult due to the scarring that occurs from radiation.

"Finding better markers for detecting cancer as it begins and then monitoring the course of treatment is a major goal of the NCI and this research in head and neck cancer is an excellent example of the type of collaborative study between two NIH institutes that helps advance the field," said NCI Director, John E. Niederhuber, M.D.
It is estimated that more than 34,000 Americans will be diagnosed with cancer of the oral cavity and pharynx (the middle part of the throat that includes the soft palate, tonsils, and tongue) in 2007, and that 7,550 Americans will die from it. Alcohol and tobacco use are the most important risk factors for head and neck cancers, with tobacco use accounting

for 85 percent of the cases. Just last month, other NIH-supported doctors reported that sexual transmission of human papillomavirus is strongly associated with throat cancer, especially in cancers arising from the tonsils and base of the tongue.

In the largest long-term study of its kind, NIH and University of Michigan researchers tested the blood of 30 patients who had undergone chemotherapy and radiation treatment for advanced throat cancer. Starting immediately before treatment and continuing every three months for 12 months, the researchers tested the patients' blood for five proteins that, in previous studies, had been found to occur at heightened levels in head and neck cancer patients. These include two cytokines known as Interleukin (IL)-6 and IL-8, and three growth factors known as growth-related oncogene (GRO)-1, vascular endothelial growth factor (VEGF), and hepatocyte growth factor (HGF). These cytokines and growth factors play an important role in the body's inflammatory response and in the growth of cells and new blood vessels. Because the researchers used a bioassay technology that can simultaneously analyze the concentrations of each protein, only a small amount of blood was required for the test.

The majority of the patients had a complete response to therapy. Patients whose blood levels of these cytokines and growth factors dropped and remained low following treatment were more likely to continue in remission. Patients who experienced large increases in protein levels were more likely to exhibit a return of the cancer or to die from it. For example, large increases in IL-6, VEGF, and HGF concentrations over time yielded a 3.8-fold, 3.0-fold, and 2.9-fold higher risk of dying of throat cancer, respectively. Patients with an increase in three or more factors were at highest risk for dying of throat cancer — more than twice as likely as patients with an increase in two or fewer factors. Finally, patients with the sharpest rises in protein levels had lower chances for survival, with patients who had a history of smoking experiencing the largest spikes. (For this reason, estimates of relative risk of death were adjusted to exclude the compounding effects of smoking.)

Because the production of these growth factors and cytokines is controlled by the same "master switch" — a regulator protein known as nuclear factor kappa B (NF-kappaB) — the researchers suggest that this protein may represent a new target for drug therapy. Drugs that help turn off NF-kappaB are currently being tested in clinical trials at NIH and elsewhere.
The researchers note that a few of the patients experienced elevations in cytokine levels related to other illnesses or injuries, and not to throat cancer; therefore, they caution that further studies are needed in larger groups of patients to confirm if this could be a useful tool to monitor for cancer, infection, or other complications. In addition, because IL-6, IL-8, VEGF, and HGF have been detected in the blood of patients with breast, cervical, ovarian, and other cancers, they suggest that this technique may have broader application in the monitoring of other forms of cancer. Further studies would need to be performed on patients with these types of cancer as well.

HUMAN ANTIBODIES PROTECT MICE FROM AVIAN FLU -- An international team of scientists, including researchers from the National Institute of Allergy and

Infectious Diseases (NIAID), part of the National Institutes of Health, report using antibodies derived from immune cells from recent human survivors of H5N1 avian influenza to successfully treat H5N1-infected mice as well as protect them from an otherwise lethal dose of the virus.

"The possibility of an influenza pandemic, whether sparked by H5N1 or another influenza virus to which humans have no natural immunity, is of serious concern to the global health community," says NIAID Director Anthony S. Fauci, M.D. "If the success of this initial study is confirmed through further laboratory and clinical trials, human monoclonal antibodies could prove to be valuable therapeutic and prophylactic public health interventions for pandemic influenza."

The research, to be published May 29 in PLoS Medicine, represents a three-way collaboration among Kanta Subbarao, M.D., and her coworkers at NIAID; Antonio Lanzavecchia, M.D., and colleagues from the Institute for Research in Biomedicine, Bellinzona, Switzerland; and Cameron Simmons, Ph.D., from the Oxford University Clinical Research Unit, Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam.

Four Vietnamese adults diagnosed with H5N1 influenza infection between January 2004 and February 2005 agreed to donate blood soon after they had recovered from their illness. In Switzerland, Dr. Lanzavecchia extracted antibody-producing white blood cells, called memory B cells, from the Vietnamese samples and treated them with a process he developed so that they rapidly and continuously produced large amounts of antibody. Next, researchers in Dr. Subbarao's lab screened 11,000 antibody-containing samples provided by the Swiss team and found a handful able to neutralize H5N1 influenza virus. Based on these results, Dr. Lanzavecchia purified the B cells and ultimately created four monoclonal antibodies (mAbs) that secrete H5N1-specific neutralizing antibodies.

Dr. Subbarao and her coworkers first tested whether the human H5N1 mAbs could protect mice from severe H5N1 infection. Groups of five mice received either of two human H5N1 mAbs at one of three dosages or human mAbs against diphtheria or anthrax. One day later, the mice were exposed through their noses to lethal doses of H5N1 influenza virus.

All the control mice — those receiving non H5N1 mAbs — rapidly developed severe illness and died within a week. In contrast, all the mice that received the first H5N1 mAb tested — regardless of dose — survived, while 80 percent of mice receiving the highest dose of the second H5N1 mAb survived. Additional tests showed that mice receiving either of the two protective H5N1 mAbs had levels of virus in the lungs that were 10 to 100 times lower than those in control mice, and little or no virus moved beyond the lungs.

The investigators also tested the therapeutic potential of the human H5N1 mAbs. Using blood products from influenza survivors is an old idea, the researchers note. During the

flu pandemic of 1918-19, for example, physicians took serum from recovered flu patients and gave it to new victims; recent historical research indicates that those blood transfusions, when given early in the illness, sometimes saved recipients' lives.

In their study, Dr. Subbarao and her colleagues infected groups of mice with a lethal dose of an H5N1 virus that had circulated in Vietnam in 2004. A total of 60 mice were given one of the four H5N1 mAbs at 24, 48 or 72 hours after infection while a control group received non-influenza mAbs. All the mice in the control group died within 10 days of infection, while 58 of the 60 treated mice survived. All four H5N1 mAbs conferred robust protection. Most surprisingly, says Dr. Subbarao, the survival rate was excellent even when treatment was delayed for three days.

Spurred by these results, the NIAID investigators next tested whether the H5N1 mAbs might be used to treat mice infected with a related but distinct H5N1 virus. Although the four mAbs used in the experiment originated after infection with the 2004 H5N1 virus, three of them nevertheless prevented the mice from dying when given 24 hours after they were infected with a 2005 H5N1 virus. This suggests, the researchers say, that human mAbs may provide broad protection against variant H5N1 viruses — a desirable quality in any therapeutic aimed at the constantly evolving flu virus.

Taken together, the findings from this international collaboration are encouraging, says Dr. Subbarao. They show that fully human mAbs with potent H5N1 influenza virus neutralizing ability can be rapidly generated from the blood of convalescent patients and that these mAbs work well to both treat H5N1 infection and prevent death from such infection in a mouse model. The authors plan to take the research forward by scaling up the production of H5N1 mAbs and, if the technique proves safe and effective in additional animal tests, to evaluate these human mAbs in clinical trials in humans.