THE CSTE WASHINGTON REPORT

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EDITOR'S NOTE: A Ugandan drug trial's findings that the AIDS medication nevirapine is effective and safe in preventing HIV transmission from mother to unborn child during birth were well-supported, according to a new, independent analysis by the Institute of Medicine of the National Academies. The IOM's analysis of the design and methodology of the 1997 drug study in Uganda, called HIVNET 012, determined that policy-makers and other scientists can rely on the resulting data and conclusions, despite some flaws in record keeping and procedural issues."The data from the HIVNET 012 study, which showed that nevirapine effectively prevents many infants from contracting HIV from their infected mothers, are sound and reliable," said James Ware, chair of the committee that wrote the report, and professor of biostatistics, Harvard School of Public Health, Boston. "None of the shortcomings that we discovered upon reviewing the data and conducting our own original analysis of source documents indicates a need to retract or discount the study's findings. Our confidence in the trial's data and findings is based on several factors, including evidence that the study's design was both scientifically sound and ethically implemented, that participants adhered well to the treatment regimens, and that a high percentage of participants remained in the study so that the effectiveness and

safety of the drug could be thoroughly assessed"– 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

HOUSE APPROPRIATIONS SUBCOMMITTEE HOLDS HEARING ON PANDEMIC FLU PREPARATIONS -- The House Labor-HHS-Education Subcommittee on Appropriations held an April 12th hearing on U.S. pandemic flu preparations, particularly the progress and shortcomings in influenza vaccine research, production and distribution. The three witnesses that testified were: Julie Gerberding, MD, MPH, Director, Centers for Disease Control and Prevention; Anthony Fauci, MD, PhD, Director National Institute for Allergy and Infectious Diseases; and Bruce Gellin, MD, MPH, Director, HHS National Vaccine Program. Dr. Fauci said the most important advantage of cell-based cultures is the ability to surge more doses and/or to change direction mid-course to produce a different vaccine strain. However, he noted that while the timeframe should be shortened with cell-based production, it still will take several months to produce a useable flu vaccine. Dr. Gellin said there is a need to incentivize manufacturers to adopt the cell-based process. But some Members of the Appropriations Subcommittee were not satisfied with the expected shortage of flu vaccine for the coming 2005-2006 flu season and pushed the speakers for solutions. Dr. Gerberding said remedying the problem requires a comprehensive solution, that demand for vaccines is unpredictable and that it would take many years to build a vaccine plant. Rep. Nita Lowey (D-NY) requested a report from HHS on what it would take to expand resources to allow for the creation of additional vaccine plants in the U.S. Dr. Gerberding also stressed the need for better global detection and response capabilities to protect everyone, including US citizens.

HHS BEGINS EFFORT DESIGNED TO DIVERSIFY AND ACCELERATE VACCINE PRODUCTION TO ENHANCE PANDEMIC PREPAREDNESS-- HHS Secretary Mike Leavitt announced April 1 that the Department has awarded a $97 million contract to Sanofi Pasteur to speed the production process for new influenza vaccines for the U.S. The five-year award supports the development of advanced techniques using a cell-based, rather than an egg-based, approach to producing influenza vaccines. The contract also calls for plans to establish a U.S.-based, cell cultured influenza vaccine manufacturing facility.

"This action begins the process of speeding up influenza vaccine production, improving surge capacity and scaling up U.S. manufacturing capability," Secretary Leavitt said. "As a result, this should allow the U.S. to have influenza vaccines in a more timely, less laborious manner, and it provides another tool for responding to and controlling a global influenza pandemic."

Currently licensed influenza vaccines are produced in chicken eggs in a process that takes nearly nine months. Scientists must first select the virus strains that they anticipate will be the predominant strains circulating in the U.S. during the following season. These strains are then adapted to grow in eggs. Manufacturers inject each adapted virus strain separately into millions of fertilized eggs, which are subsequently incubated to produce influenza virus. Large batches of these eggs are harvested and blended into a single vaccine product that includes all three influenza virus strains.

Using a cell culture approach to producing influenza vaccine offers a number of benefits. Vaccine manufacturers can bypass the step needed to adapt the virus strains to grow in eggs. In addition, cell culture-based influenza vaccines will help meet surge capacity needs in the event of a shortage or pandemic, since cells may be frozen in advance and large volumes grown quickly. U.S. licensure and manufacture of influenza vaccines produced in cell culture also will provide security against risks associated with egg-based production, such as the potential for egg supplies to be contaminated by various poultry-based diseases. Finally, the new cell-based influenza vaccines will provide an option for people who are allergic to eggs and therefore unable to receive the currently licensed vaccines.

Cell-based influenza vaccines use mammalian cells to grow the influenza viruses used in the vaccine. Under this contract, Sanofi Pasteur, a part of the Sanofi Pasteur Group, will develop, scale-up, and manufacture clinical investigational lots of inactivated influenza vaccines using human cells. These vaccines will be tested in human clinical trials in adult, elderly, and pediatric populations within the U.S. In addition, Sanofi Pasteur will develop plans for a U.S. manufacturing facility capable of producing at least 300 million doses of a pandemic influenza vaccine using this technology.

This contract is one of several contracts that HHS has awarded during the past year to enhance pandemic influenza preparedness and the annual influenza vaccine supply. Earlier awards were made to increase domestic influenza vaccine capacity, secure year round vaccine raw materials and supplies, and develop pandemic-like vaccine candidates for clinical evaluation.

This contract follows the August 2004 release of the draft National Pandemic Influenza Preparedness and Response Plan, which outlines a coordinated national strategy to prepare for and respond to an influenza pandemic. The draft plan may be found online at http://www.hhs.gov/nvpo/pandemicplan and is a result of years of work by the Department.

FINDINGS FROM PERINATAL HIV PREVENTION STUDY IN UGANDA ARE VALID, NEW REVIEW SAYS -- A Ugandan drug trial's findings that the AIDS medication nevirapine is effective and safe in preventing HIV transmission from mother to unborn child during birth were well-supported, according to a new, independent analysis by the Institute of Medicine of the National Academies. The IOM's analysis of the design and methodology of the 1997 drug study in Uganda, called HIVNET 012,

determined that policy-makers and other scientists can rely on the resulting data and conclusions, despite some flaws in record keeping and procedural issues.

"The data from the HIVNET 012 study, which showed that nevirapine effectively prevents many infants from contracting HIV from their infected mothers, are sound and reliable," said James Ware, chair of the committee that wrote the report, and professor of biostatistics, Harvard School of Public Health, Boston. "None of the shortcomings that we discovered upon reviewing the data and conducting our own original analysis of source documents indicates a need to retract or discount the study's findings. Our confidence in the trial's data and findings is based on several factors, including evidence that the study's design was both scientifically sound and ethically implemented, that participants adhered well to the treatment regimens, and that a high percentage of participants remained in the study so that the effectiveness and safety of the drug could be thoroughly assessed."

Previous evaluations of HIVNET 012 left lingering uncertainties about the trial's results, suggesting the need for a definitive, objective review. The IOM focused on the scientific validity of the study's conclusions based on a close examination of how researchers from Johns Hopkins University and Uganda's Makerere University conducted the trial. This independent review was requested and funded by the National Institutes of Health, which also funded the original trial in Uganda.

The committee did not evaluate the trial's oversight by the National Institutes of Health. It also did not examine the impact of other recent studies of potential toxicity or resistance buildup associated with the use of nevirapine either in short- or long-term treatment of HIV-infected individuals.

Because of inconsistencies in and challenges to previous audits, the committee undertook its own assessment of the accuracy and completeness of the trial's reporting through a review of medical records and other primary source documents for a subset of 49 infants involved in the trial. In addition, the committee reviewed information provided by NIH, the original investigators, previous audits of the trial, and other information brought to its attention. The findings of the HIVNET 012 study previously underwent audits by Westat Corp. and by NIH's Division of AIDS (DAIDS).

The Hopkins and Makerere researchers' conclusion that nevirapine is effective is supported by data on rates of survival and HIV infection among newborns in the study, the committee determined, noting that the trial researchers accurately recorded that information in the database created for the study. No evidence was found that the trial researchers either failed to report or mistakenly reported the deaths of any of the infants.

Regarding the trial researchers' findings on nevirapine's safety, the committee's review of source documents for the subset of 49 infants found that deaths, hospitalizations, and serious adverse events observed during clinic visits also were recorded accurately in the trial database. In some instances, however, not all serious adverse events that occurred simultaneously were reported, and some less-serious adverse events were underreported.

However, there was no evidence of a difference in the level of underreporting of adverse events among patients receiving nevirapine versus those receiving zidovudine, a second AIDS drug that also was studied in HIVNET 012. The trial investigators' comparative findings on safety are valid, the committee said.

Questions in previous audits about whether any adverse events had been missed stemmed from the trial investigators' use of a narrow but acceptable interpretation of what counted as "serious." The Hopkins and Makerere researchers used hospitalization as the principal -- but not sole -- determinant to classify clinical events as "serious" to take into account the high prevalence of malaria, tuberculosis, and other concurrent health problems in Uganda. The IOM report finds that the investigators' use of a narrow interpretation was reasonable, but it means that other researchers may not be able to generalize the study's total rate of adverse events to all settings. Other settings -- such as countries with lower rates of endemic diseases -- may have different thresholds for hospitalization and interpretations of what counts as "serious."

Another concern about HIVNET 012 focused on whether cases of jaundice -- or hyperbilirubinemia -- among infants in the study were underreported. While the study investigators reported only one infant with abnormal levels of bilirubin, a subsequent safety report issued by DAIDS initially stated that there were 63 cases of elevated bilirubin. DAIDS later retracted the safety report as incorrect. The IOM committee, based on its own analysis, determined that the DAIDS safety report initially used an incorrect upper limit of the normal range for bilirubin levels in newborns. When the correct upper limit is applied, the trial data confirm the original HIVNET 012 investigators' findings and the subsequent DAIDS retraction.

Overall, the Hopkins and Makerere researchers conducted the trial ethically and in accordance with U.S. and international standards for research and management of patient care, the IOM report says. Although there were some problems with full documentation of compliance with all the requirements for the trial, the committee determined that the HIVNET 012 study was designed and implemented with approval from the boards that oversaw the trial's design and protocols; that the researchers enrolled women only after they gave free and informed consent; and that fathers were involved in the consent process when they were reasonably available.

Blood tests that detected the presence of nevirapine in mothers and infants and other data showed that trial participants received the right drug and there was a high level of adherence to the treatment regimens, the committee found. It also noted that trial investigators achieved high rates of retention and follow-up among participants.

The committee found no reason that medical journals should revise or retract articles that reported on the efficacy and safety of nevirapine for reducing mother-to-child transmission of HIV based on the HIVNET 012 trial.

The Institute of Medicine is a private, nonprofit institution that provides health policy advice under a congressional charter granted to the National Academy of Sciences.

MEDICARE TAKES MAJOR STEP TOWARD IMPROVING QUALITY OF CARE--Medicare took another major step April 7 to improve health care quality and protect the Medicare Trust Fund by launching an ambitious billion dollar program that will provide consumers with better information on the quality of care they receive and reward providers for the quality of care they deliver.

Mark B. McClellan, M.D., Ph.D., administrator of the Centers for Medicare & Medicaid Services (CMS), said reporting, improving and rewarding quality will be at the heart of the 8th Statement of Work for the Quality Improvement Organizations (QIOs), a nationwide network of contractors dedicated to improving quality of care for Medicare beneficiaries.

"Focusing on quality will keep Medicare strong for generations to come," Dr. McClellan said. "The Quality Improvement Organizations can help health care providers succeed in the new environment of public reporting and pay-for-performance, and this in turn significantly raises the quality of care for Medicare beneficiaries."

The 8th SOW will help providers assess and report performance on measures of clinical quality, and improve their performance through important changes in how patient care is delivered. To begin this effort, CMS is releasing today a request for proposals (RFP) for this 8th Statement of Work. The RFP requests organizations to bid for the 3-year contracts that support the 8th SOW.

The quality improvement effort will focus attention on four settings – nursing homes, home health agencies, hospitals, and physician offices. It will also help protect beneficiaries and the Medicare Trust Fund through work on appeals, beneficiary complaints, payment error and other case review activities, such as the Hospital Payment Monitoring Program (HPMP). In addition, work will also focus around electronic health records and electronically transmitted prescribing, which will give patients better coordination of care.

These activities ensure Medicare pays only for those services that are medically necessary and appropriate for the patient's health care needs while also making sure quality information is used to educate providers in ways to improve care. Lastly, it will address safety and quality of services provided as a result of the new Medicare pharmaceutical benefit in January 2006.

Specifically, the effort seeks to support providers in making dramatic improvements in:

* Clinical performance measures for pressure ulcers, physical restraints and management of depression in nursing homes;
* Acute care hospitalization reduction;

* The use of telehealth in home health agencies;
* Hospitals' adoption of highly effective and efficient quality improvement strategies, such as standardized, effective processes of care;
* Physician office care of patients with chronic disease and preventive services needs, especially those working with underserved populations and physician offices' production; use and reporting of electronic clinical information; and adoption of care management such that they can report and improve on a set of expanded clinical and utilization measures that are expected to be part of public and private pay-for-performance (P4P) programs;
* Medication use, including safety and effectiveness; and
* Processes identified through expert medical review of beneficiary complaint cases and wider utilization of dispute resolution (mediation) of quality of care issues.

"The key factor that will lead to better health care over the next decade is the effective generation and use of information about the quality of health care services," Dr. McClellan said.

"Patients will use this information to make informed choices about their treatments and their providers. Providers will use this information to improve their decisions about the care provided. And policymakers will use this information to ensure that financial incentives support the best care possible," Dr. McClellan said.

The 8th Statement of Work builds on accomplishments under the current 7th Statement of Work, which laid the foundation for public reporting of provider performance through the Nursing Home Quality Initiative, the Home Health Quality Initiative, and the Hospital Quality Initiative.

Under the current contracts, providers in these settings have been able to show statistically significant improvements nationwide by working with QIO assistance, including:

* Nursing homes increased the quality of care in all states and on average were able to show relative improvement in reducing the use of physical restraints by 23 percent, and long-term (chronic) care prevalence of pain in long stay residents by 38 percent.
* Home health agencies showed improvement in management of oral medications helping to reduce patient's pain that interfered with activity.
* Hospitals, working with QIOs and others, showed an average improvement in the timeliness of administering antibiotics prior to surgery of 35%, and an average improvement of 210% in the rate and timeliness of screening for and administering influenza vaccines in patients hospitalized for pneumonia.

There are 53 QIO contracts, one for each local independent organization covering each of the 50 states, the District of Columbia , Puerto Rico, and the Virgin Islands . Funds to support QIO work are apportioned from the Medicare Trust Fund, and work is conducted through a three year performance-based contract cycle.

“Our goal is to promote care that improves safety, effectiveness, efficiency, patient-centeredness, equity, and timeliness,” said William Rollow, M.D., director of the Quality Improvement Program at CMS. “Through these contracts, QIOs will work with providers, partners and stakeholders to accomplish this and transform healthcare quality.”

The first Statement of Work for this contract was introduced in 1982 with a focus on case review. National quality improvement was introduced in the 7th Statement of Work.

CMS today also announced that it is requesting public comments on the potential design of the Medicare Health Care Quality Demonstration. Section 646 of the Medicare Modernization Act requires the demonstration, which is to encourage the delivery of improved quality of patient care through increased efficiency. CMS will ask for demonstration proposals later this year. Further information may be obtained online at www.cms.hhs.gov/researchers/demos/mma646/default.asp or by writing on-line to mma646@cms.hhs.gov.

FDA ASKING FOR PUBLIC COMMENT ON FOOD LABEL CHANGES -- The Food and Drug Administration (FDA) April 1 asked for public comment on two proposals to improve the appearance and content of the nutrition label to help consumers make better-informed weight management decisions. The proposals focus on providing practical serving size information and increasing the prominence of calories on the food label.

The proposals are direct responses to the recommendations contained in the FDA's Obesity Working Group (OWG) report entitled "Calories Count." The OWG final report made short and long-term recommendations that are based on the scientific fact that weight control is mainly a function of caloric balance.

"Today's action demonstrates our commitment to make the food label more meaningful and helpful to consumers," said Dr. Robert Brackett, Director of FDA's Center for Food Safety and Applied Nutrition. "We are interested in exploring how modifying the food labeling regulations might give consumers better information they can use to control and manage their weight."

In the first Advanced Notice of Proposed Rule Making (ANPRM), *Food Labeling; Prominence of Calories*, FDA is requesting comments on how calories appear on packaged food and how consumers use this information in making healthier dietary choices. Additionally, the agency is seeking comment on the reformulation of the foods or redesign of packaging that may occur if any changes are made to the food label.

The second ANPRM, *Food Labeling: Serving Sizes of Products that Can Reasonably Be Consumed At One Eating Occasion; Updating of Reference Amounts Customarily Consumed (RACCs); Approaches for Recommending Smaller Portion Sizes,* addresses the issue of serving size information on the food label, as well as possible ways to revise the label that would make it easier for consumers to choose more healthful foods. In the

ANPRM, FDA is asking if changes should be made requiring that pre-packaged foods reasonably consumed during one eating occasion state the nutrition information for the entire package. For example, a 20-ounce soda would be required to list the total amounts of its nutritional content on the labeling.

Both of the ANPRMs have an open comment period for 75 days. Interested persons can submit comments, referencing the docket number, electronically to fdadockets@oc.fda.gov or in writing to the Division of Dockets Management, 5630 Fishers Lane, room 1061, Rockville, MD 20852.