THE CSTE WASHINGTON REPORT

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EDITOR'S NOTE: A new report on childhood asthma released December 12 by the Centers for Disease Control and Prevention (CDC) shows that death rates for asthma among children under age 18 have declined since 1999, while doctor visits for the condition have more than doubled over the past decade. In 2005, nearly 9 percent of children - 6.5 million children under age 18 - were reported to currently have asthma. The percentage of children who had asthma more than doubled between 1980 and 1995, from 3.6 percent to 7.5 percent. In 2001, CDC introduced a more precise measurement of asthma and the five years since then the trend has remained stable at historically high levels-- 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

SENATOR HARKIN URGES HEALTH AND EDUCATION GROUPS TO FIGHT FOR ADDING BILLIONS MORE IN FY 2007 – Despite the recent announcement by the new Democratic Chairs of the House (Rep. David Obey, WI) and Senate (Sen. Robert Byrd WV) Appropriations Committees that they intend to fund all unfinished FY 2007 appropriations bills at the FY 2006 level in a year-long continuing resolution, Senator Tim Harkin, the new Chairman of the Senate Subcommittee on Labor-HHS-Education Appropriations, is urging health and education groups to keep the pressure on to obtain billions more in funding. Last March, a coalition of these groups, working with Sen. Harkin and Sen. Specter (R-PA), the out-going Chair of the Subcommittee and now Ranking Minority Member, were successful in winning 73 votes for a Specter-Harkin amendment budget amendment that committed $7 billion over the Presidents' FY 2007 budget request for the programs funded under the Labor-HHS-Education Appropriations bill. A similar effort in the House won an allocation for the Subcommittee that was $4 billion higher than the President's FY 2007 budget request with a promise from then Majority Leader Boehner to Moderate Republicans to provide the additional $3 billion before final passage. Neither the House nor the Senate completed their respective Labor-HHS-Education Appropriations measures which are now subject to the decision to fund them at the FY 2006 level in a year-long continuing resolution. Sen. Harkin told groups that approach, plus a promise to strip out all special Congressional projects known as earmarks, should free up between $2-$12 billion for programs for all 9 of the unfinished bills, given the overall cap of $873 billion for FY 2007. While it is expected that at least $3 billion will be devoted to Veteran's healthcare, and at least $200 million in the Labor-HHS-Ed bill must be used to increase a scheduled pay raise for Social Security Administration employees, there may be additional funding available for other programs. In response to his appeal, health groups are currently pressuring House and Senate leaderships, and Appropriations principals in both parties to honor votes and promises made in the 109th Congress. They have the rest of January to effect a result; the year-long continuing resolution is expected to be completed by February 15th.

CDC REPORTS BINGE DRINKING IS COMMON AMONG HIGH SCHOOL STUDENTS AND TIED TO OTHER RISKY BEHAVIORS -- Binge drinking is common among high school students in the United States and is strongly associated with sexual activity, violence, and other risky behaviors, according to a new study, Binge Drinking and Associated Health Risk Behaviors Among High School Students, released by the Centers for Disease Control and Prevention (CDC) and published in the January 2007 issue of Pediatrics.

The study analyzed data from the 15,214 high school students who completed the 2003 Youth Risk Behavior Survey. CDC scientists found 45 percent of the students reported past-month alcohol consumption, and 64 percent of students who drank reported binge drinking (defined as having five or more drinks of alcohol in a row). High school boys and girls who drank alcohol had similar rates of binge drinking ? 67 percent and 61 percent, respectively. Among students who engaged in binge drinking, 69 percent reported doing so on more than one occasion in the past 30 days.

The researchers also found that the likelihood of engaging in other risk behaviors - including sexual activity, smoking, and physical fighting - was greater for binge drinkers than for drinkers who did not binge and for nondrinkers.

“Our study clearly shows that it’s not just that students drink alcohol, but how much they drink that most strongly affects whether they experience other health and social problems,” said Dr. Jacqueline Miller, Medical Officer on the CDC’s Alcohol Team and the lead author of the report. “It also underscores the importance of implementing effective strategies to prevent underage and binge drinking, such as enforcing the minimum legal drinking age and reducing alcohol marketing to youth, which can help us change social norms regarding the acceptability of underage and binge drinking.”

Compared to nondrinkers, drinkers who did not binge drink were more than twice as likely to be sexually active; more than four times as likely to smoke cigarettes; and more than twice as likely to have been in a physical fight. And the likelihood was greater still for binge drinkers. Binge drinkers were more than five times as likely as non-drinkers to be sexually active; more than 18 times as likely to smoke cigarettes; and more than four times as likely to have been in a physical fight. The likelihood of engaging in these and other risky behaviors, including marijuana use and suicide attempts, increased with the frequency of binge drinking. Binge drinking was also strongly associated with poor school performance.

For more information about alcohol and binge drinking, visit the CDC’s Division of Adult and Community Health’s Web site at http://www.cdc.gov/alcohol/index.htm.

STATE OF CHILDHOOD ASTHMA, UNITED STATES: 1980-2005 -- A new report on childhood asthma released December 12 by the Centers for Disease Control and Prevention (CDC) shows that death rates for asthma among children under age 18 have declined since 1999, while doctor visits for the condition have more than doubled over the past decade.

In 2005, nearly 9 percent of children - 6.5 million children under age 18 - were reported to currently have asthma. The percentage of children who had asthma more than doubled between 1980 and 1995, from 3.6 percent to 7.5 percent. In 2001, CDC introduced a more precise measurement of asthma and the five years since then the trend has remained stable at historically high levels.

Other highlights:

After increasing steadily between 1980 and 1998, asthma death rates among children have for the most part declined since 1999. A change in the way causes of death are coded resulted in a sizable one-year decline between 1998 and 1999, but since then the asthma death rate for children has fallen from 3.2 deaths per 1 million children under age 18 in 1999 to 2.5 deaths per 1 million in 2004.

Asthma-related visits to physician offices have increased sharply since the early 1990's, from less than 40 visits per 1,000 children under age 18 in 1990 to 89 visits per 1,000 in 2004.

Among race/ethnic groups, Puerto Rican and non-Hispanic black children were reported

to have the highest percentages of asthma (19.2 and 12.7 respectively).

According to 2003 data, children with at least one asthma attack in the previous year (nearly 4 million children) missed a cumulative total of 12.8 million school days due to asthma.

Asthma-related emergency department visits for children have remained fairly stable from 1992 to 2004 (103 visits per 10,000 children in 2004 compared to 97.6 visits per 10,000 in 1992).

Among the 37 states for which data were available, the states with the highest percentage of children with asthma were: Massachusetts, Hawaii, Oklahoma, Maryland, and Rhode Island. The states with the lowest percentage of children with asthma were: Utah, California, Iowa, Tennessee, and Washington.

"The State of Childhood Asthma, United States: 1980-2005" is available at www.cdc.gov/nchs.

SCIENTISTS DISCOVER HOW MATERNAL SMOKING CAN CAUSE CLEFT LIP AND PALATE -- Scientists supported by the National Institute of Dental and Craniofacial Research (NIDCR), part of the National Institutes of Health, report that women who smoke during pregnancy and carry a fetus whose DNA lacks both copies of a gene involved in detoxifying cigarette smoke substantially increase their baby's chances of being born with a cleft lip and/or palate.

According to the scientists, about a quarter of babies of European ancestry and possibly up to 60 percent of those of Asian ancestry lack both copies of the gene called GSTT1. Based on their data, published in the January issue of the *American Journal of Human Genetics*, the scientists calculated that if a pregnant woman smokes 15 cigarettes or more per day, the chances of her GSTT1-lacking fetus developing a cleft increase nearly 20 fold. Globally, about 12 million women each year smoke through their pregnancies.

Dr. Jeff Murray, a scientist at the University of Iowa and senior author of the study, noted that parents who are considering having a child and need added motivation for the mother to quit smoking might one day be tested to determine their GSTT1 status. Because the fetus inherits its genes from both mother and father, the test would determine the likelihood of the baby developing without the GSTT1 gene to detoxify the cigarette smoke.

"A test that indicates the GSTT1 gene is present certainly would not eliminate a baby's risk of a cleft because many other genetic and environmental factors can be involved." said Murray. "But the opposite result would give the mother one more compelling reason to quit smoking for her own health and for the sake of her child."

In the United States, about one in every 750 babies is born with isolated, also called nonsyndromic, cleft lip and/or palate. The condition is correctable but typically requires several surgeries. Families often undergo tremendous emotional and economic hardship during the process, and children frequently require many other services, including complex dental care and speech therapy.

According to Murray, researchers have built a strong statistical case over the past several years that pregnant women who smoke put their unborn babies at greater risk of developing a cleft. The data raised two related questions. "Do genetic variations in the mother influence her own metabolism of the cigarette smoke and its byproducts, thus setting in motion developmental changes that cause the cleft in the fetus? Or do genetic variations in the fetus itself compromise its ability to metabolize the cigarette smoke and cause the cleft?" said Dr. Min Shi, now a scientist at NIH's National Institute of Environmental Health Sciences and a lead author of the paper.

To find the answers, Murray's group teamed with colleagues in Denmark to perform a large, complex, and possibly first-of-its-kind international study. The group first assembled a list of 16 genes of interest, each of which encode proteins that plug into various pathways in the body involved in detoxifying dangerous chemicals. "We picked genes that previous evidence shows either are directly involved in cigarette smoke toxicity or are major players in general toxicity management in people," said Dr. Kaare Christensen, a scientist at the University of Southern Denmark in Odense and an author on the paper.

"These genes tend to be quite variable from person to person in their precise DNA structure, or spelling," Christensen added. "We wanted to see if any of these variations might adversely affect a person's ability to break down the toxic products of cigarette smoke."

Christiansen and his colleagues then turned to their existing database of kids with clefts, their parents, and siblings. In all, the scientists analyzed 5,000 DNA samples from both continents — including 1,244 from children born with clefts. Importantly, the families in Denmark and Iowa provided the opportunity to independently confirm the findings in two distinct populations.

In addition, they had free public access to the NIDCR-funded COGENE project, a comprehensive online database of genes expressed throughout the various stages of development. Working closely with Dr. Mike Lovett at Washington University in St. Louis, one of COGENE's founders, the database proved especially helpful because cleft lip and/or palate occurs during the first 5-to-12 weeks of development. This meant the scientists had to be sure not only that their genes of interest are expressed during this vital period but are switched on in fetal craniofactial structures. If the genes met both criteria, the investigators said they hoped their subsequent data might point them to a gene-environment interaction.

As reported, the scientists determined from their analyses that the mother provides the toxic environmental exposure, which then can be greatly amplified by the genetics of the fetus to produce the cleft. This marks the first time a gene-environment interaction in clefting has been documented at a molecular level. The data also point the way for future studies to define the specific molecular chain of events that lead to the cleft, vital information to understand and hopefully one day prevent the process.

While sifting through the data, the researchers took particular note of the GSTT gene and its contribution to clefting. The gene encodes one of the body's approximately 20 different glutathione S-transferase enzymes. These enzymes collectively play roles in common detoxification processes, ranging from chemically altering drugs and industrial chemicals to detoxifying polycyclic aromatic hydrocarbons, a key component of cigarette smoke.

The scientists found that pregnant women who smoked and also carried fetuses that lacked the GSTT1 enzyme were much more likely to give birth to a baby with a cleft. This finding was true in Iowa and Denmark, and they noted in the COGENE database that the gene is highly expressed in developing craniofacial structures. "It may be that be that the lip and palate can form normally without GSTT1," said Murray. "But if the chemicals in cigarette smoke challenge the normal development of these structures, fetuses that lack the gene are at a distinct disadvantage."

Murray and his collaborators continue their genetic analyses. "We now have data from about 350 genes on this cohort of families," he said. "It's certainly a more complicated analysis to perform, but we're working our way through it and hope to have some very interesting data in the months ahead."

The article is titled "Orofacial Cleft Risk is Increased with Maternal Smoking and Specific Detoxification-Gene Variants," and is published in the January 2007 issue of the *American Journal of Human Genetics*. The authors are Min Shi, Kaare Christensen, Clarice R. Weinberg, Paul Romitti, Lise Bathum, Anthony Lozada, Richard W. Morris, Michael Lovett, and Jeffrey C.Murray.

NEW DETAILS ON HOW THE IMMUNE SYSTEM RECOGNIZES INFLUENZA

-- Drawing upon a massive database established with funds from the National Institute of Allergy and Infectious Diseases (NIAID), one of the National Institutes of Health (NIH), scientists have completed the most comprehensive analysis to date of published influenza A virus epitopes--the critical sites on the virus that are recognized by the immune system. The findings, reported by researchers at the La Jolla Institute for Allergy and Immunology (LIAI), are being published online this week by the journal *Proceedings of the National Academy of Sciences*.

The study should help scientists who are designing new vaccines, diagnostics and immune-based therapies against seasonal and pandemic influenza because it reveals in molecular detail exactly where the immune system focuses on the viruses. Although the

complete molecular structures of essentially all major strains of influenza viruses are known, immune responses concentrate on limited regions of certain parts of the virus, and these regions must be identified as immune epitopes by research studies. The LIAI team found that while there were hundreds of shared epitopes among different virus strains, including the avian H5N1 virus, only one has been published that appears ideal for multi-strain vaccines. Information on shared protective epitopes is important for developing influenza vaccines that can provide broad protection against multiple strains of the virus.

“This study is interesting for what it shows we know and do not know,” says NIAID Director Anthony S. Fauci, M.D. “It reveals many gaps in our knowledge of influenza viruses and indicates where we need to focus our attention.”

The analysis drew upon a much larger effort called the Immune Epitope Database and Analysis Resources Program, which began in 2004 after NIAID awarded LIAI a $25 million contract to create a single repository of immune epitopes from critical disease-causing microbes, including agents that might be used in a bioterrorist attack. Influenza epitopes comprise only a portion of the extensive database, which has become the largest single collection of such information anywhere in the world. It includes data from thousands of separate articles published over several decades, providing extensive dossiers on dozens of pathogens.

“The purpose of the database is to provide a catalog of molecules and structures that scientists around the world can quickly access and use to understand the immune response to a variety of epitopes, or methodically predict responses to as-yet untested targets,” says Alessandro Sette, Ph.D., who heads the Vaccine Discovery division at LIAI and is the lead investigator on the project.

For the current study, Dr. Sette and his colleagues examined 600 different epitopes from 58 different strains of influenza A virus. One of their main goals was to determine how conserved, or similar, epitopes are between different strains of bird and human influenza viruses. Knowing this is important because the virus rapidly mutates and can swap gene segments between strains, which could increase the ability of an avian virus to be transmissible to humans.

In addition, only a handful of the epitopes are known to be associated with protective immunity. Most of the influenza virus epitopes in the database are those recognized by a type of immune cell known as a T cell; far fewer are recognized by B cells, a type of white blood cell that produces infection-fighting antibodies. Antibodies induced by seasonal and pandemic flu viruses or vaccines are a major component of immunity that protects against these viruses.

Strains of influenza virus can vary enough in their neutralizing B cell epitopes that a vaccine against one strain may not protect against another strain. But if epitopes are conserved between virus strains, the immunity a person has developed towards one strain might provide at least some protection against the other strain.

Using a software tool they developed, the LIAI team found hundreds of conserved influenza virus epitopes in the database, including those between avian H5N1 and strains of human influenza viruses. But what is less clear from the analysis is how cross-reactive an immune response would be to most of these conserved epitopes. Further analyses may assist scientists in identifying vaccine targets that might offer broader protection and in predicting how effective a new vaccine will be.

Other analyses revealed major gaps in scientists' knowledge about influenza viruses. Of the 600 epitopes in the database, for instance, very few were from strains of H5N1 avian influenza. And even though the database contains epitopes from all the influenza virus' proteins, the vast majority of the data relates to just two influenza proteins, the hemagglutinin (HA) and nucleoprotein (NP).

Most of the influenza virus data comes from analyses of immune responses obtained with mice; some comes from rabbits, ferrets and monkeys, and very little comes from humans or birds. In fact, only one antibody epitope came from a human. The LIAI researchers say more studies should be focused on identifying human T and B cell epitopes from human and avian strains of influenza virus — especially those associated with protective immunity.

"The bottom line is that this study shows us where we need to go," says project director Stephen Wilson, Ph.D., chief technology officer at LIAI. "Hundreds of flu epitopes have already been published and are now in the database, but critical gaps become apparent when one looks for human antibody targets."

Plans for the future include adding data on epitopes that are involved in autoimmune diseases and epitopes that trigger allergic and asthmatic reactions. Dr. Sette and his colleagues have also built numerous tools for analyzing and visualizing the data and for predicting immunity against different pathogens — all of which is publicly accessible on their website (see http://immuneepitope.org).
For more information on influenza see http://www3.niaid.nih.gov/news/focuson/flu. Also visit http://www.PandemicFlu.gov for one-stop access to U.S. Government information on avian and pandemic.