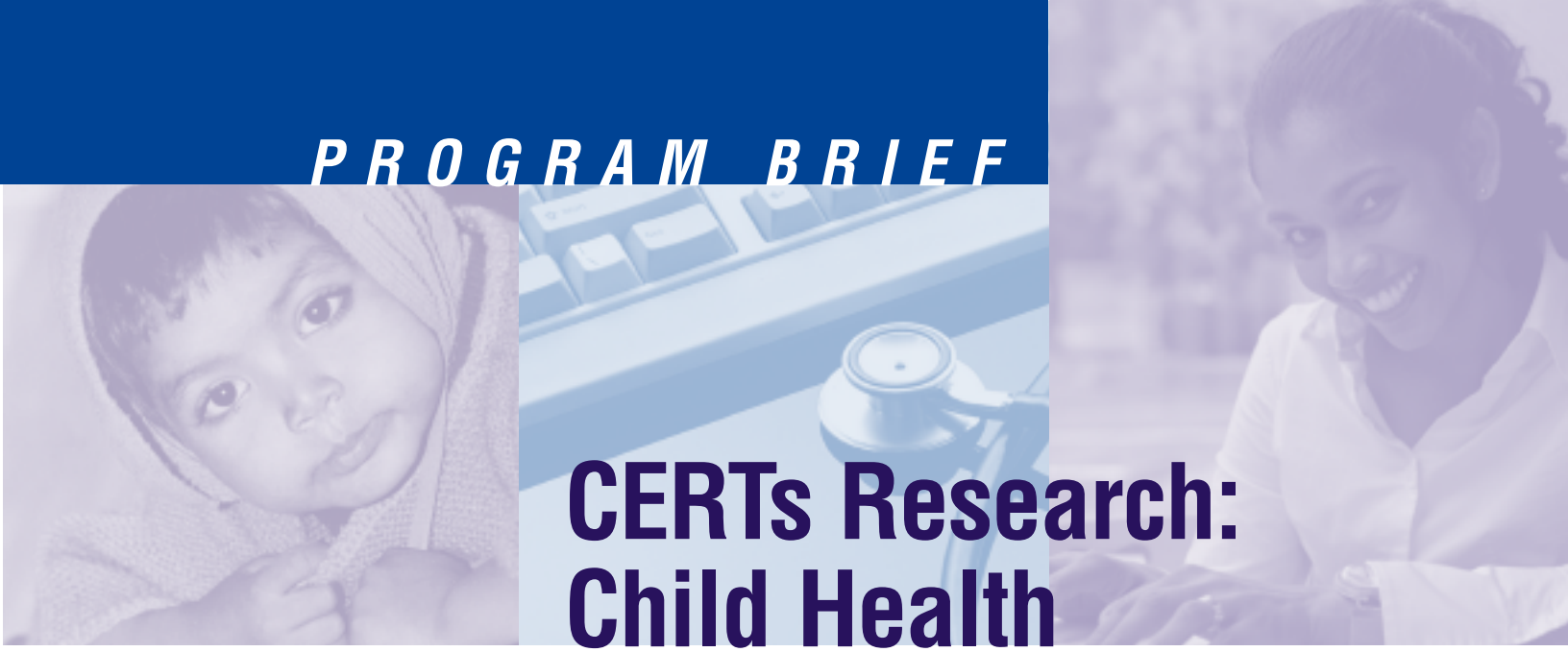
PROGRAM BRIEF



CERTs Research: Child Health

Agency for Healthcare Research and Quality

AHRQ's mission is to improve the quality, safety, efficiency, and effectiveness of health care by:

- Using evidence to improve health care.
- Improving health care outcomes through research.
- Transforming research into practice.

Background

The mission of the Centers for Education & Research on Therapeutics (CERTs) program is to conduct research and provide education that will advance the best use of therapeutics (drugs, medical devices, and biological products). The program seeks to increase awareness of the benefits and risks of new, existing, and combined uses of therapeutics, thereby improving the effectiveness and safety of their use.

The program is administered as a cooperative agreement by the Agency for Healthcare Research and Quality (AHRQ), in consultation with the U.S. Food and Drug Administration (FDA). The CERTs receive funds from both public and private sources, with AHRQ providing core financial support. The CERTs comprise seven centers (see box), a Coordinating Center, a Steering Committee, and numerous partnerships with public and private organizations. Collectively, the CERTs have more than 40 unique data sources and serve as a national resource of experienced researchers.

CERTs Program Centers

Each center focuses its educational and research efforts on therapies in a particular population or therapeutic area:

- *Duke University Medical Center*—Therapies for disorders of the heart and blood vessels
- *HMO Research Network*—Drug use, safety, and effectiveness in health maintenance organization populations
- *University of Alabama at Birmingham*—Therapies for musculoskeletal disorders
- *University of Arizona Health Sciences Center*—Drug interactions that result in harm to women
- *University of North Carolina at Chapel Hill*—Therapies for children
- *University of Pennsylvania School of Medicine*—Therapies for infection; antibiotic drug resistance
- *Vanderbilt University Medical Center*—Prescription drug use in a Medicaid population

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CERTs and Child Health

Since the inception of the CERTs program in September 1999, the centers have developed a portfolio of more than 200 completed and ongoing studies with results that have addressed important issues regarding the best use of therapies. Several of these projects are related to child health and one CERTs center, the University of North Carolina at Chapel Hill (UNC) center, is devoted solely to studying therapies for children.

The Best Pharmaceuticals for Children Act was passed by the U.S. Congress in 2001 and provides several avenues to test drugs in children. Despite this legislation, an estimated 80 percent of prescription drugs given to children have not been tested on this population and are not labeled for pediatric use. Children are not "small adults." They have different metabolic rates, their bodies change rapidly, and their ability to understand and express information varies widely. Research is needed to describe how children respond to individual medications and to different treatment regimens.

The CERTs projects are aimed at advancing knowledge; informing health care providers, patients, and policymakers about that knowledge; and improving aspects of the health care system related to therapeutics. The following are examples of CERTs studies that are relevant to children.

Advancing Knowledge

The CERTs study the beneficial and potentially harmful effects of medical therapies in children so that parents and providers can make informed decisions about treatments.

Evaluating drugs in children with HIV.[1] The "recommended prescribed dose" of a drug may work very well for many patients but not for others because of underlying differences from patient to patient, including differences in the way drugs are absorbed and metabolized. Less is known about these individual differences in children than in adults. Children may also metabolize drugs differently as they grow and develop. These differences may mean that the "recommended" dose may not have the treatment effect a sick child needs. HIV provides an important example. More than 20,000 children and teenagers in the United States may be infected with human immunodeficiency virus (HIV). How they respond to given doses of anti-HIV drugs such as protease inhibitors may differ from how adults respond.

Therapeutic drug monitoring (TDM) is a way of measuring individual patients' response to drugs and tailoring drug doses to individual patients' needs. The UNC center has assessed the concentrations of protease inhibitors in the blood of children infected with HIV. Concentrations that are too high can be toxic, and concentrations that are too low can cause the virus to become resistant to the drug. The group used a separation technique (high-pressure liquid chromatography) to develop a test for measuring four of the most commonly used protease inhibitors in blood samples. In a pilot study, they found that in a group of 15 pediatric patients taking at least one of the medications, 4 children, or 27 percent, had no detectable protease inhibitors in their blood plasma. One child had a suspiciously high concentration, suggesting that the patient had taken an incorrect amount of medication, or that the patient may have had abnormal metabolism of the drug.

The UNC center is now engaged in a larger study to further explore the best ways to use TDM to tailor the

treatment of HIV-infected children, to promote ways to get the best effect for each individual child.

Blood glucose monitoring of children with type 1 diabetes. Controlling blood glucose levels closely can prevent or delay the serious complications of diabetes due to low insulin production, yet controlling glucose too closely can lead to episodes of hypoglycemia severe enough to cause unconsciousness. Children are more susceptible to hypoglycemia than adults, but they are less able than adults to recognize and respond to early symptoms of hypoglycemia.

The UNC center is conducting a study among children and adolescents with type 1 diabetes to determine whether continuous glucose monitoring devices can help reduce hypoglycemia while maintaining good blood glucose control. The devices have a small sensor that is inserted under a patient's skin and connected to a pager-sized monitor. They measure glucose every few minutes. While continuous glucose monitors have been used in adults for nearly two decades, experience in children is very limited. This study should assist physicians in deciding whether continuous glucose monitoring is feasible, well tolerated, and beneficial in children and adolescents with type 1 diabetes.

Prenatal and early erythromycin exposure and pyloric stenosis.[2,3] Pyloric stenosis is a narrowing of the lower part of the stomach caused by enlarged muscles in the pylorus. This prevents food from emptying out of the stomach and can cause forceful vomiting or lead to dehydration. Approximately 3 in 1,000 infants in the United States have the condition.

The cause of pyloric stenosis is unclear, but evidence indicates that it may result from exposure to the commonly prescribed antibiotic, erythromycin. The Vanderbilt center conducted two studies to determine whether infants who had been exposed to erythromycin prenatally or in the first 90 days of life were more likely to develop pyloric stenosis. Patients in the study included mothers and infants in Tennessee's Medicaid program, TennCare.

The researchers found that exposure to erythromycin in infants 3 to 13 days old was associated with an increased risk of stenosis, but exposure either prenatally or after 13 days was not. This evidence provides practitioners with useful information to weigh the risks and benefits of prescribing erythromycin for infants and expectant mothers.

Effect of tetracycline on bacterial resistance.[4] It is believed that long-term use of antibiotics by patients plays a role in the development of organisms that are resistant to multiple antibiotics. Individuals with acne are a natural population for studying the effects of long-term antibiotic use since they are generally young, healthy patients who are sometimes exposed to antibiotics for prolonged periods.

The University of Pennsylvania center explored whether long-term use of tetracycline, a commonly prescribed acne medicine, affected bacterial populations in the throats of adolescents and young adults with acne. Researchers found that patients taking tetracycline were more likely to have the bacteria Streptococcus pyogenes in their throats than those not taking the drug. Further, the S. pyogenes in the tetracycline-treated patients were more likely to be resistant to at least one antibiotic than those in patients not taking tetracycline.

These results suggest that long-term use of an antibiotic for treating acne could lead to antibiotic resistance in regions of the body, such as the throat, known to be a potential site of more serious systemic infections.

Increased antibiotic-resistant pathogens in Hispanic children. To further explore antibiotic resistance in children, the UNC center led a project that addressed whether antibiotic resistance can vary according to ethnicity. They started by reviewing clinical laboratory and medical records of children with urinary tract infections at the UNC clinics from 1996 to 2003. The types and frequency of urinary tract infection pathogens, their patterns of susceptibility to different antibiotics, and patient clinical and demographic data were tracked.

Of the Escherichia coli bacteria for which there were antibiotic sensitivity data, only 54 percent were pan-susceptible, meaning treatable with several different antibiotics. Among white children with an E. coli infection, 47 percent could be treated with several antibiotics, and for African-American children, the rate was 60 percent. But among Hispanic children, the rate of infection with pan-susceptible bacteria was only 20 percent.

The next phase of the project includes testing children in community pediatric clinics, especially those serving Hispanic children. Results should help to assess whether resistance rates at UNC clinics are similar to those in the community and should also lead to a better understanding of risk factors.

Informing Patients and Providers

Understanding the risks and benefits of medical therapies is critical to improving the safety and effectiveness of their use. It is also critical to ensure

that practitioners, patients, and their guardians have the knowledge needed to use medical therapies appropriately.

Asthma improvement strategies. From 1982 to 1996, the prevalence of asthma increased 38 percent in children under the age of 18. The UNC center has made it a goal to give local physicians and their patients the tools they need for the best management of asthma.

The center developed an educational effort to share knowledge about strategies for improving care of children with asthma that includes a 3-hour continuing medical education session for physicians and a learning collaborative within a North Carolina Area Health Education Center region. The educational program has been adopted as a statewide Medicaid demonstration project.

Tools for diagnosing and managing ADHD. The UNC center is committed to providing physicians, children, and parents with resources to better diagnose and manage attention deficit hyperactivity disorder (ADHD). It is estimated that between 3 percent and 5 percent of children have ADHD.

The UNC center has helped create a Web site (http://www.nichq.org/resources/toolkit/) that provides an online toolkit for parents, teachers, and health care providers of children who have ADHD. The toolkit provides the best evidence on the diagnosis, treatment, and management of ADHD in an easy-to-use format.

Online resource to prevent arrhythmia. Long QT syndrome is a hereditary disorder of the heart's electrical rhythm that can occur in otherwise-healthy people. The incidence of children with congenital long QT syndrome is approximately 1 in 5,000, and those with the condition are at very high risk of sudden death due to arrhythmia. Since there are more than 50 drugs that can precipitate an arrhythmia in children, the Arizona center developed a Web site (www.torsades.org) to use as a reference to routinely review children's medications for possible risk.

Antibiotic use among children.[5] CERTs research frequently uncovers therapeutic areas where antibiotics are prescribed more often than needed, which increases the risk for antibiotic-resistant bacteria. But in a recent study, the HMO Research Network center found that antibiotic use dropped in one area. Between 1996 and 2000, there was a significant drop in the number of antibiotics prescribed to children ages 3 months to 17 years. In previous years, from 1977 through the early 1990s, antibiotic use in children had increased.

In 1998, the Centers for Disease Control and Prevention, working with other national and State organizations, began to actively promote more judicious prescribing for children. They based their efforts on results from a group of studies that tested the impact of education programs on parents and providers. The CERTs conducted one study of 16 towns in Massachusetts (REACH Mass), testing the effectiveness of certain education programs on parental knowledge, actual antibiotic use, and incidence of resistant organisms. The results were encouraging: there was a drop in antibiotic prescriptions for children, which suggests that it is possible to effectively educate both health care providers and patients about the dangers of overusing antibiotics.

Improving the System

The CERTs' broadest reaching and potentially most beneficial efforts are

those that improve aspects of the health care system. A number of projects are aimed at increasing the efficiency of health care, making pediatric therapies safer, and giving health care providers better access to current treatment information.

Prevalence and prevention of rickets.[6] Rickets was a common disease in the United States during the Industrial Revolution. Recognizing that vitamin D helped to prevent rickets led to a drop in the number of cases, and by the 1960s, physicians rarely saw patients with the disease.

In the 1990s, however, the prevalence of rickets increased, and UNC researchers wanted to better understand the reason why. Examining data about children in the North Carolina Women, Infants, and Children Program (WIC), the researchers found that all the rickets cases among pediatric patients were in dark-skinned children who were breast fed and who did not receive vitamin D supplementation. The darker an infant's skin, the more sun exposure the infant needs to synthesize vitamin D.

The study's findings caused an immediate change in North Carolina public health practice. The North Carolina Pediatric Society requested that the State of North Carolina distribute a multivitamin supplement free of charge to any exclusively breastfed infant or child older than 6 weeks. Funding for the supplementation was provided through a Maternal and Child Health Block Grant and distributed through the Supplemental Nutrition Program for Women, Infants, and Children. During a 16-month period, more than 1,500 children received this supplementation at a cost of about $1.50 per month per child. Fact sheets were also developed to help educate parents and health professionals about the need for vitamin D supplementation for breastfed infants and children.

Recommendations for safe prescribing for children. The UNC center worked with the United States Pharmacopeia (USP) to develop recommendations for safe prescribing for children. The USP publishes legally recognized standards of strength, quality, and purity for drugs and other therapeutic products. Together, UNC and the USP studied more than 5,600 medication errors reported by more than 500 hospitals to the USP's anonymous Web-based reporting system, MEDMARX[SM]. They considered the error reports and the best published evidence on the causes of and solutions for pediatric medication errors.

Based on this information, five sets of recommendations about all phases of medication use were made. The topics ranged from packaging and storing, to prescribing and administering medications to pediatric patients. In April 2003, the USP published the recommendations on its Web site: http://www.usp.org/patientSafety/tools/pedRecommnds2003-01-22.html. The recommendations can be used by all health care providers who treat children.

Prescription drug use in pregnant women.[7,8] Using medications during pregnancy poses a potential risk to both the mother and fetus. To alert physicians and pharmacists about the possible risks of prescribing medications during pregnancy, the FDA uses a risk classification system for drugs taken while pregnant. The risks of drugs in category C are unknown, drugs in category D have known risks that may be outweighed by their benefits, and those in X have definite risks that outweigh benefits. Using the FDA's

classification system as a guide, the CERTs have conducted several studies to learn more about the frequency of such prescriptions.

To assess how often unborn babies are exposed to drugs that may cause them harm, the HMO Research Network center recorded drug use before and during pregnancy for 152,531 women in eight different health systems and geographic regions. Of these women, 71,913–or almost half–were prescribed drugs that fall within categories C, D, and X of the FDA's risk classification system. The HMO Research Network center study suggests that a significant number of pregnant women are prescribed drugs that present unknown or harmful risks.

The Vanderbilt center has also looked at the use of prescription drugs during pregnancy, focusing on drugs in the FDA's category X. The group looked at how many of 95,284 pregnant women in TennCare filled prescriptions for category X medications. Within the group, 391 filled such prescriptions, meaning that about 4 in 1,000 fetuses were exposed to potentially harmful medication. Women over the age of 35 and women enrolled in TennCare because of disabilities were more likely to fill category X prescriptions during pregnancy than other categories of pregnant women. Study results underscore the need to inform both physicians and women so they can consider the risks in taking these medications during pregnancy.

Looking to the Future

The CERTs continue to conduct research and develop educational projects that study and report the efficacy, safety, and use of various medical therapies in children. Because so little is known in this area, the CERTs face great challenges but great opportunities as well.

For More Information

The CERTs welcome input about the types of research and education needed to better address costs, effectiveness, and safety issues related to the use of therapeutics. More information on the CERTs program is available from ARHQ's Center for Outcomes and Evidence:

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