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ON BEHALF OF THE AMERICAN ACADEMY OF PEDIATRICS

"Antibiotic Resistance and the Impact on the Health of Children: the Need for More Safe and Effective Antibiotics and Better Antimicrobial Stewardship"

COMMITTEE ON ENERGY AND COMMERCE HEALTH SUBCOMMITTEE
U.S. HOUSE OF REPRESENTATIVES

June 9, 2010

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Good morning. I appreciate the opportunity to testify today before the House Energy and Water Subcommittee on Health regarding antimicrobial resistance. My name is John Bradley, MD, FAAP, and I am proud to represent the American Academy of Pediatrics (AAP), a non-profit professional organization of more than 60,000 primary care pediatricians, pediatric medical sub-specialists, and pediatric surgical specialists dedicated to the health, safety, and well-being of infants, children, adolescents, and young adults.

I currently am the Chief of the Division of Infectious Diseases, Department of Pediatrics at the University of California, School of Medicine and the Clinical Director of the Division of Infectious Diseases at the Rady Children's Hospital San Diego. I am a member of American Academy of Pediatrics' Committee on Infectious Diseases and the Infectious Diseases Society of America's (IDSA's) Task Force on Antimicrobial Drug Availability.

As prior witnesses have spent a great deal of time and attention on defining the increasing problem of antibiotic resistance among humans – including statistics on numbers of adult and pediatric patients infected by resistant bacteria and the financial impact on the US healthcare system outlined by the IDSA just moments ago – my comments will focus more specifically on the challenges it presents to the health of pediatric populations.

Children Are Not Little Adults

Infectious diseases have a significant impact upon American children. Children contract infections more often than adults and are more likely to spread infections to playmates, schoolmates, siblings, parents and grandparents.

Our recent national experience with the 2009 H1N1 influenza, as well documented by the Centers for Disease Control and Prevention (CDC), provides a striking picture of just how vulnerable children are to infection, and how quickly infections can be spread in communities by infants and school-aged children. Both viral infections and bacterial infections, including those caused by antibiotic-resistant bacteria, have been documented to

spread easily among children and from children to adults. Antibiotic-resistant bacterial pathogens have the potential to cause widespread injury and suffering, and even death, in children.

Perhaps one of the most pressing reasons to find better ways to address the uncontrolled spread of antibiotic resistance is that damage to the child lasts a lifetime. A school-aged child with a devastating bone infection that involves the growth plate will never have normal growth of his or her leg, will need multiple corrective surgeries, and will never quite regain normal function. Worse, the death of a child from antibiotic-resistant bacteria in 2010 is an unpardonable tragedy. With all our resources and expertise in prevention, as well as drug discovery and development, it is unconscionable not to have an effective therapy for each and every bacterial infection.

Concerns Specific to Infants and Children

Antibiotic-resistant bacteria are increasingly prevalent in hospitals as well as in the community. Newborn infants are a particularly vulnerable target for bacterial infections, as their immune systems are immature and suppressed to assure growth in the womb. In the United States, approximately 12% of infants are born prematurely. Premature infants are being successfully cared for at lower and lower birth weights, with many infants born now who weigh only a single pound having a good chance for survival. However, these premature infants' skin and major organ systems are not fully developed, leading to an even greater susceptibility to infections of the skin, lung and intestines. And because many of these very premature infants must remain in the Neonatal Intensive Care Unit for weeks and they require a number of life saving procedures, they are at risk for infection with bacteria which survive in the NICU because they are resistant to antibiotics.

In addition, many infants are born with anatomic defects that require aggressive and extensive corrective surgeries very early in life in order to survive. These infants may spend many weeks in the hospital as they adapt to life with their newly constructed

anatomy. Infants with congenital heart disease represent one such group that are at high risk of post-operative wound infections after major open-chest and open-heart reconstructive surgery.

Young children with certain genetically inherited diseases may not survive to adulthood due to chronic and recurrent infections caused by antibiotic-resistant bacteria. The most well-known of these pediatric disorders are cystic fibrosis and chronic granulomatous disease. These children are extremely susceptible to recurrent infections requiring many courses of antibiotics, and ultimately are infected by multi-drug resistant bacteria, mycobacteria, and fungi that are exceedingly challenging to treat.

Certain infections are unique to children due to developmental and growth characteristics. One such infection is called acute hematogenous osteomyelitis, or bone infection. This infection is characteristic of young adolescents whose bones are growing at their fastest rates, who are very active and continually sustain minor injury to their bones and joints during normal daily physical activity and sports.

Staph bacteria are the most common cause of infections, and over the past 10 years many major pediatric centers in the United States have now documented a dramatic rise in bone infections caused by a new, antibiotic-resistant strain of staph, called MRSA (methicillin-resistant *Staphylococcus aureus*). While reports from every pediatric hospital in the United States document the increased destruction of bone and muscle tissue caused by MRSA, the most dramatic and life-threatening complications occur when MRSA spreads to the bloodstream.

The most detailed published reports concerning MRSA infections have come from Texas Children's Hospital in Houston. In one case, a child with a bone infection in his leg who was not responding to antibiotic treatment actually required a filter to be surgically implanted in his veins to trap the bacteria as they entered his bloodstream from his infected legs. This extreme measure was necessary to prevent MRSA from spreading to his lungs,

where the bacteria were creating an increasing number of large abscesses and progressive pneumonia, putting the child's life in danger.

Many of the bacteria that cause infections in adults also cause infections in neonates, infants and children, including not only the previously mentioned MRSA bacteria, but also the ESKAPE bacteria (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *ESBL positive E. coli*).[1]

Several recent reports now document an increasing and very disturbing trend regarding the significant impact that antibiotic resistance bacteria are having on the health of children. A report published this year from the National Children's Medical Center in Washington, DC, documented that MRSA bacteria infections in the neonatal intensive care unit were responsible for increasing the length of hospital stay by a mean of 40 days, and were associated with an average extra charge of $164,301 per baby.[2]

Last year, a report from a neonatal intensive care unit in Long Island, New York, provided information about the spread of a highly antibiotic-resistant *Acinetobacter baumannii*.[3] This bacterium was recovered from 7 neonates, 4 of whom died. All affected neonates were born between at 23 to 26 weeks of gestation (approximately 6 months) and weighed between 430 and 720 grams (1 to 2 pounds) at the time of exposure to *Acinetobacter*, which was resistant to all commonly used antibiotics for the newborn. While the bacteria were susceptible to only one FDA-approved antibiotic for newborn infants, this antibiotic has never been studied systematically in such premature infants, forcing pediatricians to use an antibiotic for which no safety or efficacy data are available.

Another study[4] published in a manuscript last year investigated the rise of antibiotic resistant (ESBL) *E. coli* and *Klebsiella* (two of the ESKAPE bacteria) in children in the Salt Lake City region, and documented a three-fold increase between 2003 and 2007.

Another article from the Pediatric Intensive Care Unit at Johns Hopkins University Medical Center in Baltimore published in December of 2008[5] documented the entry into their unit of vancomycin-resistant enterococcus (VRE), a resistant organism that has primarily been associated with infections in adults. When these investigators began systematically looking for this resistant organism in babies, they found a rate that was 5 times higher than they previously suspected.

While *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* primarily cause infections in hospitalized patients, certain other bacteria tend to cause more disease in otherwise healthy children living in communities. Antibiotic-resistant community pathogens with particular impact for children include MRSA and *Streptococcus pneumoniae* (the most common cause of ear infections, sinus infections, and pneumonia and often referred to as "pneumococcus"). Even with appropriate use of antibiotics to treat bona fide infections in children, pneumococcal bacteria will develop resistance.

Stopping the spread of drug resistant infections among infants and children presents a unique challenge. Good personal hygiene, especially thorough hand-washing, usually keeps infections from spreading between adults who have runny noses, coughs, sneezes, and even diarrhea; however, these good health habits are not part of normal behavior for toddlers and young school-aged children.

National strategies to combat the rapid spread of H1N1 influenza actually included the closing of some child care centers and schools to prevent community transmission. When this type of isolation strategy was implemented in the United States, the predicted spread of influenza in communities dramatically slowed. Numerous outbreaks of bacterial and viral infections have commonly been reported in child care centers. In a recent November 2009 report[6], the CDC described 639 documented infections caused by antibiotic-resistant *Shigella* dysentery originating in daycare centers in northwest Missouri. These bacteria were resistant to both ampicillin and trimethoprim-sulfamethoxazole, the antibiotics most commonly used to treat these microbes, forcing doctors to use antibiotics that are not FDA-

approved for these infections, including the fluoroquinolones, a class of antibiotic that carries a specific caution for cartilage damage in children.

The Role of Vaccinations

As previously detailed, all infants below the age of 2 years are particularly susceptible to bacterial and viral infections due to immature immune systems. Vaccination is one important component of combating the spread and severity of antimicrobial resistant infections.

The AAP has taken pride in being the professional pediatric organization that has for decades developed and promoted an immunization schedule recommended for all children in the United States. Over the past several years, collaboration with the CDC has strengthened the clinical and pharmaceutical science behind the recommendations, building on the careful work of the FDA in its evaluation of the safety and efficacy of each and every vaccine for both children and adults.

The AAP aggressively promotes universal vaccination through its Committee on Infectious Diseases and supports the recommendations of the CDC's Advisory Committee on Immunization Practices for the prevention of the most common and deadly bacterial infections: *Haemophilus influenzae* (meningitis, pneumonia), pneumococcus (meningitis, pneumonia, ear and sinus infections), meningococcus (meningitis) and pertussis (whooping cough), as well as universal immunization to prevent a number of viral infections including influenza and chickenpox.

Increased vaccinations are making a positive difference. Universal protection of children through certain immunizations (protein-conjugated pneumococcal vaccines) has actually decreased antibiotic resistance in the targeted bacteria that continue to circulate in communities. An unexpected but welcome benefit of immunizing infants is the documented decrease in antibiotic-resistant infections in parents and grandparents.

Prior to universal immunization of all infants with vaccines for the most aggressive of these infections, our hospital used to treat over 100 children per year with meningitis, many of whom suffered permanent brain damage. We now treat only about 3 such children each year. However, the few we see are more likely to have an infection with a bacterium resistant to the antibiotics which in the past were capable of successfully treating the infection.

But vaccines alone will not solve this problem in children. There is a critical need for additional vaccines for other types of antibiotic-resistant bacteria, both common and uncommon strains. While the vaccine for pneumococcus that is recommended by the AAP for universal immunization for children has decreased the numbers of children hospitalized with pneumonia and meningitis, it has had far less of an impact on decreasing the number of children with ear infections. Antibiotic-resistance continues to be a problem with ear infections, forcing doctors to use higher dosages of antibiotics and alternative antibiotics to those that were available even 10 years ago.

Perhaps even more frightening is the fact that pneumococcal bacteria continue to evolve under selective pressure from vaccines and antibiotics, and new, antibiotic resistant strains have emerged that now cause extensive, invasive disease across the United States.[7] New vaccines will hopefully address current issues concerning these new resistant strains, but we are bracing for the evolution of yet newer, resistant bacterial strains. Antibiotic resistance is a moving target, and requires ongoing intense commitments to develop better surveillance tools, better vaccines, and better antibiotics.

Efforts to Promote Appropriate and Judicious Use of Antibiotics

Approximately three quarters of all outpatient prescriptions of antimicrobial agents for children are given for five conditions: otitis media, sinusitis, cough illness/bronchitis, pharyngitis, and nonspecific upper respiratory tract infection (the common cold).

Antimicrobial agents are prescribed, even though many of these illnesses are caused by viruses and are unresponsive to antimicrobial therapy. Physicians report that many patients and parents try to persuade them to dispense unnecessary antimicrobial agents.

As early as January 1998, the American Academy of Pediatrics published, with the CDC, a series of 6 articles in the Academy's official journal, *Pediatrics*, on the Judicious Use of Antimicrobial Agents for Upper Respiratory Tract Infections, in which guidelines were published that challenged the common practice of using antibiotics for sore throats, runny noses and coughs. To minimize the development of antibiotic resistance, pediatricians were urged to use antibiotics only when a true bacterial infection was present, and only for the shortest duration necessary to cure the infection. The AAP Committee on Infectious Diseases continues to promote appropriate use and guidance in their regularly published "Red Book," which is used by pediatricians and many other providers of health care for children.

The AAP, working with their partners including the CDC, has designed and promoted educational materials for pediatricians and for parents. Information that every sore throat does not need to be treated with antibiotics represented a significant challenge to pediatricians who every day face countless sick children and their concerned parents, and know that the vast majority of these children have viral infections and do not need antibiotics. These patient-oriented materials were designed to be shared with parents in waiting rooms and exam rooms, in order to change the parents' and grandparents' expectations during pediatric clinic visits. The AAP assists pediatricians in their efforts to educate parents so that they do not simply go to another provider who will prescribe antibiotics inappropriately.

Collaborations with Other Professional Organizations

The Academy's members include pediatricians who are trained and certified in the field of infectious diseases. Most of these members are also members of the Infectious Diseases

Society of America (IDSA). Many pediatric members of the IDSA are putting extensive efforts into the IDSA's initiatives that are designed to develop safe and effective new antimicrobial therapy for all ages. Those of us who are pediatricians place a particular emphasis on the safety of new drugs for newborns, infants and children.

AAP also works in close partnership with a wide range of other professional organizations on these issues, including the American Medical Association, American Academy of Family Physicians, the National Association of Pediatric Nurse Practitioners, the American Public Health Association, and many others.

The AAP supports the many and diverse antimicrobial resistance programs within the CDC, National Institutes of Health (NIH), and Food and Drug Administration (FDA), as well as public-private partnerships, global collaboration, and work in the pharmaceutical and diagnostics industries to incentivize the development of new antimicrobial agents (e.g., the IDSA's 10 X '20 Initiative). At the same time that we are creating incentives for the development of new antibiotics, we must create an environment for appropriate use of newly developed agents that will allow for the maximum effects of the new agents over the longest possible period of time. It is not a simple task to create new antimicrobial drugs, and it is our obligation to children that we avoid the inappropriate and possibly harmful use of available antibiotics.

Legislative Opportunities

The AAP supports legislation that will define and limit the spread of antibiotic-resistant organisms. H.R. 2400, the Strategies to Address Antimicrobial Resistance, or STAAR, Act, introduced by Committee member Rep. James Matheson (D-UT) and currently cosponsored by Committee members Reps. Tammy Baldwin (D-WI), Donna Christensen (D-VI), and Gene Green (D-TX) creates a comprehensive strategy to address numerous facets of antimicrobial resistance, and provides a means to prevent the spread of antimicrobial-resistant bacteria. Through the legislation, a newly-created Antimicrobial

Resistance Office (ARO), located in the Department of Health and Human Services, would coordinate and extend the activities of many federal agencies currently involved in these efforts. Further, the STAAR Act provides for input from Advisory Panels from the academic and medical practice community to collaborate with federal officials in creating an effective and realistic program. Importantly, improved data collection on the various uses of all antimicrobials and resistance will be a key feature, allowing both federal officials and the medical community to have the information they need to focus efforts on appropriate use. Many agencies, including the CDC, FDA, and NIH currently are involved in various aspects of these issues, but it is essential to coordinate their efforts and provide them access to new tools to manage resistance more effectively.

The AAP also strongly supports the highly successful Best Pharmaceuticals for Children Act (BPCA). This legislation encourages and incentivizes research on drugs in children that would otherwise not occur. Essential data on the uses of antimicrobials and other drugs for neonates, infants and children have been accumulated through the BPCA, allowing children to receive better health care. As an example, safety studies in children on a particular class of antibiotics (fluoroquinolones), that display the potential for cartilage destruction in juvenile animals, was carried out at the request of the FDA. While these antibiotics are not routinely recommended for use in children, they are used when bacteria are resistant to other antibiotics. The manufacturers had no interest in either studying or marketing these antibiotics to children, due to the risks of toxicity that were apparent to all, and the fact that the pediatric demand for the drugs was relatively small. However, as we do use these antibiotics occasionally in all pediatric age groups, including premature infants, it was critical to assess the safety of these drugs in a systematic way. Following completion of these studies, which are available now on the FDA website, all pediatricians are aware of the potential of these drugs to cause cartilage and tendon injury and can weigh that risk appropriately against the potential benefits of use. The outstanding work of the FDA has focused this incentive program on medical questions of the highest priority for children, resulting in more than three hundred sixty drugs being re-labeled through the BPCA, many of them antibiotics.

Finally, the AAP would be remiss if we did not acknowledge the need to address antibiotic use in animal agriculture as a critical component of reducing antimicrobial resistance. The vast majority of antibiotics produced in the United States are used in livestock, often at subtherapeutic levels to promote growth. Judicious use of antimicrobial agents in humans accounts for roughly half of total antibiotic use in this country. Evidence exists that if we are to truly impact this situation, use of antimicrobial agents in food production must be addressed.[8] AAP strongly supports passage of H.R. 1549, the Preservation of Antibiotics for Medical Treatment Act, which would place reasonable limits on the veterinary use of antimicrobial drugs that are important in human medicine.

Concluding Thoughts

While increasing antibiotic resistance is a disturbing trend for all, it is especially concerning when considering infant and child populations. There is a growing need for more safe and effective antibiotics and better microbial stewardship.

The American Academy of Pediatrics commends you, Mr. Chairman, for convening this hearing today to bring added attention to the important issues surrounding antimicrobial resistance and the judicious use of antibiotics. The Academy is grateful for the Committee's commitment to child health, and we hope that you will consider us a partner and supporter in your efforts to define and limit the spread of antibiotic resistant organisms, particularly as they impact our children.

I appreciate this opportunity to testify and look forward to your questions.

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