Biodefense Meeting
Best Pharmaceuticals for Children Act
Eunice Kennedy Shriver **National Institute of Child Health and Human**
** Development**
September 8–9, 2008
6130 Executive Boulevard
Rockville, MD

This meeting was sponsored by the Obstetric and Pediatric Pharmacology Branch (OPPB), Center for Research for Mothers and Children (CRMC), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), U.S. Department of Health and Human Services (HHS), in support of the Best Pharmaceuticals for Children Act (BPCA) Program.

Meeting Goals

The goals of the meeting were to:
- Identify what additional studies may be needed to help ensure the current therapeutic agents in the Strategic National Stockpile (SNS) are properly formulated, dosed, safe, and effective for the care of children and pregnant women
- Review and provide input into further development of therapeutic countermeasures for children and pregnant women in selective ongoing basic science and clinical biodefense-related research studies.

Welcome and Biodefense Overview
David Siegel, M.D., Program Director, Chemical, Biological, Radiological, and Nuclear
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In the years since the September 11, 2001, terrorist attacks, the federal government, in collaboration with academia and industry, has developed various medical countermeasures to deal with the consequences of weapons of mass destruction (WMD). As development has continued, the acute care clinicians who would be at the front lines providing care to children and pregnant women in response to a WMD event began to notice significant gaps in available medical countermeasures for these populations. Some of the gaps are as follows:
- During the 2001 anthrax scare amoxicillin was recommended for prophylaxis. However, the results of a recent evaluation of the pharmacokinetics (PK) of amoxicillin during pregnancy suggested that the prescribed amoxicillin dosing resulted in drug levels that were inadequate to prevent anthrax during pregnancy. It was noted that the creatinine clearance of a pregnant woman is, for the most part, 150 percent of the clearance of a nonpregnant woman.
- The SNS is a national repository of antibiotics, chemical antidotes, antitoxins, life-support medications, intravenous (IV) administration devices, airway maintenance supplies, and medical/surgical items. The SNS is designed to supplement and resupply state and local public health agencies in the event of a national emergency anywhere and at anytime within the United States or its territories. CHEMPACKS are a vital part of the SNS. They are

forward deployed. They are designed to provide the antidote for nerve agent exposure as well as treat the seizures that may develop as a consequence of toxin exposure.

- Children, who are much more difficult in general to obtain vascular access, do not have, for most medications, the availability of autoinjectors (which have the capability to get through clothing).
- One biodefense therapeutic device for administering antidote to nerve agents is the pralidoxine pediatric autoinjector. The pralidoxine dosage in the autoinjectors is appropriate for adults but not for children. The autoinjectors were designed initially for military personnel. Many states differ in their policy regarding use of adult dosed autoinjectors in children.
- Regulatory issues have created challenges for deployment of appropriate biodefense medicines for children. Currently, about 80 percent of pediatric medications are used off label, which affects deployment in the federal jurisdiction.
- There is an effort to include midazolam in the CHEMPACKS. Midazolam is used for acute treatment of status epilepticus. Therapeutic levels of intramuscular (IM) midazolam are achieved much more quickly than those of IM diazepam in treating seizures. Although midazolam is used broadly to treat seizures, it is not labeled for that use.

In addition to gaps in currently available countermeasures, there are projected gaps in future countermeasures because of the problems in the current methodologies used in biodefense research and development in the care of children and pregnant women. There are a number of reasons for this situation:

- There is a lack of an obstetric/pediatric voice on key committees. Labeling children and pregnant women as special populations many times means that they will be dealt with eventually.
- Although there have been no major bioterrorist events since September 11, 2001, time is crucial. There are risks in delaying studies for pregnant women and children to determine the best biodefense countermeasures for these populations.
- In some circumstances, the pharmaceutical industry has been reluctant to produce therapeutic agents or devices for children because of lack of profitability. For example, some formulations may be approved only down to 2 years of age. There are no pediatric autoinjectors (except atropine). BPCA has provided a funding mechanism for the necessary study for pediatric labeling, but the amount provided is only a partial fix (80 percent of pediatric drugs are used off label).

The purpose of this meeting was to bring attention to the biodefense needs of children and pregnant women as well as assisting in the pointing out what studies that would be of potential benefit for their protection.

OPPB's CBRN Research Program set up five working groups composed of very talented volunteers from the federal government as well as academia. These groups and subgroups are infectious disease (vaccines; antibiotics, antivirals, and antitoxins), chemical (cyanide, nerve agents, and pulmonary agents), and radiation. Many working group members are subspecialists that have experience in research and development, whereas others are acute care clinicians with significant research experience. Working group members included "adult" representatives from

the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Neurological Diseases and Stroke (NINDS), the National Institute of Environmental Health Sciences (NIEHS), and the National Institute of Arthritis and Musculoskeletal Diseases (NIAMS). These representatives provided input on the status of basic and clinical biodefense "Adult" research. The National Library of Medicine (NLM) provided critical support to the working groups' activities.

The working groups held monthly teleconferences for the past 3 months. They reviewed currently available medical countermeasures, including the contents of the SNS. They also reviewed ongoing animal and adult clinical biodefense studies, with a focus on those involving next-generation countermeasures deemed a priority by the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE). The working groups encourage further development of devices and therapeutics that are currently approved for treatment of the adult population and are not currently available for the care of children or pregnant women because of the lack of the necessary pharmacological studies and/or regulatory and logistical issues. On occasion, the working groups have identified medical countermeasures in which adults would also benefit. The integrated adult/pediatric working groups discussed whether children and/or pregnant women should be included in new studies from the onset or whether it is more appropriate to add on these populations after initial data collection. The working groups encourage development of appropriate juvenile/pregnant animal models. Sometimes because of ethical issues, data from animal models and adult trials will have to be extrapolated when necessary. The working groups encourage development of therapeutic agents that can be used for biodefense purposes as well as for treatment of regular disease. One of the goals of the working groups is to provide advice regarding children and pregnant women to biodefense entities such as SNS leadership and BARDA.

Dr. Siegel provided an overview of specific areas of interest.

Anthrax. Anthrax is an acute disease in humans and animals caused by the bacterium *Bacillus anthracis*, which is highly lethal in some forms. Anthrax has a worldwide distribution in the natural environment. Anthrax most commonly infects wild and domesticated herbivorous mammals that ingest or inhale the spores while eating grass or browse. There are three types of anthrax: cutaneous, inhalation, and gastrointestinal (GI). Cutaneous anthrax is contracted from contact with infected fur, hides, and wool. In the natural environment, inhalational anthrax is contracted by inhaling 8,000–50,000 spores. GI anthrax is contracted by ingesting contaminated animal meat. There is no person-to-person transmission.

The incubation period for cutaneous anthrax is 1–7 days. Raised lesions resembling mosquito bites develop 2–5 days after exposure. Papular lesions progress to blisters or vesicles and then form black-scabbed lesions. Patients may have fever, malaise, lymphadenopathy, and tenderness. The mortality rate for cutaneous anthrax is about 20 percent.

The incubation period for inhalational anthrax is 1–60 days. Prodromal flu-like illness with fever, myalgia, cough, and chest pain develops 2–5 days after exposure, followed by dyspnea, diaphoresis, and cyanosis. On examination, patients present with cough, tachypnea, hypoxia, and

rales. There may be potentially septic infiltrates, pleural effusion, and appearance of meningeal signs. Initial chest x-ray may appear normal or show characteristic widened mediastinum or patchy lung. The spores create a necrotizing mediastinitis that results in the characteristic widened mediastinum. More than half of adults with inhalational anthrax develop meningitis. The patient may deteriorate rapidly and progress to shock and death in 24–36 hours. The reported mortality rate is 80 percent.

GI infection in humans is most often caused by eating anthrax-infected meat and is characterized by serious GI difficulty; vomiting of blood, severe diarrhea, acute inflammation of the intestinal tract, and loss of appetite. Some lesions have been found in the intestines and in the mouth and throat. After the bacterium invades the bowel system, it spreads through the bloodstream throughout the body, making even more toxins on the way. GI infections can be treated but usually result in mortality rates of 25–60 percent, depending on how soon treatment begins.

Smallpox. Smallpox is an infectious disease unique to humans caused by either of two virus variants named variola major and variola minor. The viruses belong to the orthopoxvirus genus. Other viruses in the genus include vaccinia, cowpox, and monkeypox. Variola virus infects only humans in nature, although primates and other animals have been infected in a laboratory setting. No known animal reservoirs of smallpox exist. Smallpox was declared eradicated by the World Health Organization in 1977 (last naturally occurring case). Historically, the highest attack rates were among household (or hospital) contacts. The highest attack rates of close contacts are unvaccinated individuals (37–88 percent). The greatest infectivity is from the appearance of rash until scabbing over of lesions. Variola virus may be isolated in saliva 5–6 days before the appearance of rash, but transmission of infection does not precede the appearance of rash. Patients are not infectious during viral prodrome.

Variola major is an incapacitating disease. Many victims are permanently scarred, and some suffer corneal scars that may cause blindness. The mortality rate is about 30 percent. In children, the mortality rate is 50–75 percent. Variola minor is a mild clinical variant and has low morbidity and mortality. Hemorrhagic smallpox can occur in any person, although there is an increased occurrence in pregnant women. It is uniformly fatal. Malignant (flat) smallpox is almost always fatal.

There is onset of fever 7–17 days after exposure (mean, 12 days) followed by 2–4 days of febrile syndrome with headache and backache before onset of rash. Enanthem appears, shortly, and is followed by the appearance of rash on face and forearms. The rash spreads to the trunk and legs. The patient is most contagious from the time rash appears until all lesions scab over. Deaths occur from viremia/toxemia. The major differential diagnosis is varicella.

Nerve Agents. Nerve agents are the most toxic of known chemical warfare agents. They are chemically similar to organophosphate pesticides (organophosphorous cholinesterase inhibitors) and exert their biological effects by inhibiting acetylcholinesterase enzymes. When a nerve agent inhibits acetylcholinesterase, acetylcholine accumulates and continues to stimulate the affected organ. The binding of the agent to the enzyme is permanent unless removed by therapy.

The nerve agents can be removed from the affected enzymes and the enzyme reactivated by several compounds, the most useful being the oximes. Medical management for nerve agent toxicity includes evaluation and support of the airway, breathing, and circulation; administration of atropine or pralidoxime; decontamination; and supportive therapy (the order is clinically dependent). Diazepam, lorazepam, or midazolam should be given to all patients with seizure activity, unconsciousness, diffuse muscle twitching, and if one or more organs are involved.

Nerve liquid agents are readily absorbed from the skin and eyes. Children absorb significantly higher levels of nerve agent compared with adults. When inhaled, nerve agents are readily absorbed in the respiratory tract. Because nerve agent vapors are generally denser than air, infants and small children are at higher risk of exposure due to their proximity to the ground. Ingestion of nerve agents is a relatively rare occurrence (not a very efficient weaponized modality), but toddlers may be more vulnerable due to their hand-to-mouth behaviors.

A child's smaller mass alone reduces the dose of chemical agent required for toxic/lethal effects. Animal studies have shown that the lethal dose of nerve agent in an immature animal versus an adult animal is 10 percent. With higher respiratory rates and minute volumes than adults, a child will inhale a greater dose of chemical agent. The smaller airway diameter, anatomic subglottic narrowing, omega-shaped epiglottic structure, relatively large tongue size, and less rigid ribs and trachea make children more vulnerable to chemical agent-induced pathology. Children are more vulnerable to these toxicants being absorbed through the skin because their skin is thinner and contains more moisture and they have a larger surface area to weight ratio than adults.

Nerve agents may penetrate the blood–brain barrier more easily in children than in adults. Children younger than 4 years of age with status epilepticus have the highest risk of death. Children may only exhibit central nervous system (CNS) effects when exposed to nerve agents. Young children, especially younger than 4 years of age, are more prone to develop seizure disorders secondary to hypoxia or other CNS insult.

Cyanide. Cyanide acts as a cellular asphyxiant. By binding to mitochondrial cytochrome oxidase, it prevents the use of oxygen in cellular metabolism. The CNS and myocardium are particularly sensitive to the cellular hypoxia induced by cyanide. In addition, oxygen remains in the blood, with resultant red-appearing venous blood. Treatment involves a two-step process: administration of amyl or sodium nitrite followed by administration of sodium thiosulfate. Amyl/sodium nitrite removes the cyanide from the cells and binds it to hemoglobin (forming methemoglobin). The sodium thiosulfate then removes the cyanide from the methemoglobin, allowing subsequent excretion.

Pulmonary Agents. A pulmonary agent is a chemical that damages the membrane in the lungs that separates the alveolus from the capillary. As a result of this damage, plasma leaks into the alveoli causing pulmonary edema. Phosgene and chlorine were the two most commonly weaponized pulmonary agents in World War I, and in many instances, they were combined in the same artillery ordnance. Chlorine gas—being water soluble—is primarily absorbed by the upper airway. Exposure to low concentrations may cause eye and nasal irritation, sore throat, and

cough. Inhalation of higher concentrations can rapidly lead to respiratory distress with bronchospasm and/or pulmonary edema.

Respiratory distress can occur immediately, with clinical findings of wheezing, rales, hemoptysis, and cyanosis. Pulmonary injury may progress over several hours. Phosgene—being only slightly water soluble—is primarily absorbed by the lower airway. Inhaling low concentrations may cause no signs or symptoms initially or symptoms that are secondary to mild irritation of the airway. In individuals who develop severe pulmonary damage, a progressive pulmonary edema may ensue, which can produce up to 1 liter of fluid per hour. Phosgene and chlorine can cause a chemical irritant-induced type of asthma called reactive airways dysfunction syndrome. Recovery is likely for a patient who survives the first 48 hours after exposure.

Treatment of exposure to pulmonary agents includes aerosolized bronchodilators for bronchospasm. Steroids may be used for intense inflammation or preemptively if the patient experienced a severe exposure, particularly phosgene. Prophylactic antibiotics are not routinely administered, but pneumonia can complicate pulmonary edema. Diuretics are contraindicated because these patients tend to be hypovolemic and hypotensive. Fluid resuscitation and dopamine administration may be necessary as well as continuous positive airway pressure.

Radiation. Ionizing radiation injures tissues through energy transfer. Outcomes include cell death, cell malfunction, and delayed effects. In cell malfunction, the cell lives but is altered and cannot repair itself, and the altered cells may contribute to tissue and organ malfunction. In delayed effects, the cell's genetic material is altered, which creates the potential for later malignancy and birth defects.

Acute radiation syndrome is a combination of clinical symptoms occurring in stages during a period of hours to weeks after radiation exposure, as injury to various tissues and organs is expressed. Acute radiation syndrome requires high radiation and exposure of penetrating ionizing radiation to the whole body or a large portion of the body delivered acutely. Acute radiation syndrome may involve hematological, GI, cutaneous, and neurovascular systems. Long-term exposure outcomes may include renal failure and pulmonary fibrosis.

The amount of radiation absorbed by the body—the absorbed dose—determines how sick a patient will be. Biodosimetry is the use of laboratory or clinical methods to measure or estimate the dose of ionizing radiation energy absorbed by an individual. Biodosimetry tools measure the dose to internal organs and tissues from external exposure and internal contamination.

The treatment goals for radiation sickness are to prevent further radioactive contamination, treat damaged organs, reduce symptoms, and manage pain. Other aspects of treatment include:
- Decontamination—Decontamination is the removal of as many external radioactive particles as possible. Removing clothing and shoes eliminates about 90 percent of external contamination. Gently washing with water and soap removes additional radiation particles from the skin.
- Treatment for damaged bone marrow—A protein called granulocyte colony-stimulating factor, which promotes the growth of white blood cells, may counter the effect of radiation

sickness on bone marrow. Treatment with this protein-based medication may increase white blood cell production and help prevent subsequent infections. Severe damage to bone marrow may require transfusions of red blood cells or blood platelets.

- Treatment for internal contamination—Some treatments may reduce damage to internal organs caused by radioactive particles. These treatments include potassium iodide, Prussian blue, and diethylenetriamine pentaacetic acid (DTPA).

OPPB's Role in Biodefense

Gilman Grave, M.D., Branch Chief, Endocrinology, Nutrition and Growth Branch, Acting Center Director, CRMC, NICHD, NIH, HHS

Dr. Grave explained that OPPB's primary focus is on pediatric and obstetric pharmacology research. For biodefense activities, OPPB's role is to:
- Identify gaps in current knowledge of medical countermeasures, therapeutic agents, and devices for treating children and pregnant women exposed to mass chemical, infectious disease, or radiation threats
- Review research issues
- Set priorities for feasible basic research and/or clinical studies to improve biodefense countermeasures and therapies for children and pregnant women.

Part of NICHD's mission is to ensure that all children have the chance to fulfill their potential to live healthy and productive lives free from disease or disability. In pursuit of its mission, NICHD—and OPPB in particular through the BPCA Program—will support biodefense-related research for children and pregnant women.

BPCA: Biodefense

Anne Zajicek, M.D., Pharm.D., Associate Branch Chief, Pediatric Medical Officer, OPPB, CRMC, NICHD, NIH, HHS

Dr. Zajicek gave a brief overview of the BPCA Program, which is a partnership between NIH and the Food and Drug Administration (FDA). Over the past 14 years, FDA has made several attempts to add pediatric labeling. The history of the related legislations is as follows:
- 1994 Pediatric Rule—proposed the extrapolation of adult data to children; that is, the disease process and drug efficacy in adults could be extrapolated to children
- 1997 FDA Modernization Act (FDAMA)—proposed the concept of exclusivity; that is, if FDA requested a pediatric study from a pharmaceutical company, and the company conducted the study, it was granted an additional 6 months of exclusivity on the drug's patent
- 1998 Pediatric Rule—proposed that pediatric studies be conducted prior to FDA approval of the New Drug Application (NDA)
- 2002 BPCA—proposed the reauthorization of 6-month exclusivity and a process for studying off-patent drugs; NIH became involved as a sponsor of off-patent drug studies
- 2003 Pediatric Research Equity Act (PREA)
- 2007 BPCA, PREA reauthorizations.

For BPCA 2002, a master list of all off-patent drugs that lacked adequate pediatric labeling was developed. In consultation with experts in pediatric practice and research, an annual list of drugs was developed, prioritized, and published. Considerations for prioritization include availability of safety and efficacy data, need for additional data, potential to produce health benefits, and need for reformulation, However, in the 2002 legislation, the definition of "off-patent" was unclear. Therefore, the 2007 BPCA:

- Clarified the definition of "off-patent" as a drug that has no listed patents or has one or more listed patents that have expired
- Calls for a list of priority areas in pediatric therapeutics including drugs or indications that require study
- Requires consideration of available information, including therapeutic gaps, potential health benefits, and adequacy of infrastructure for research
- Allows NIH to submit a Proposed Pediatric Study Request (PPSR) to FDA as a draft Written Request (WR).

The priority list is developed by NIH in consultation with its Institutes and Centers (ICs), FDA, the Centers for Disease Control and Prevention (CDC), pediatric subspecialists and subspecialty groups, and committees of the American Academy of Pediatrics.

In January 2003, the following drugs were on the priority list:

- Azithromycin
- Baclofen
- Bumetanide
- Dobutamine
- Furosemide
- Dopamine
- Heparin
- Lithium
- Lorazepam
- Rifampin
- Sodium nitroprusside
- Spironolactone

In April 2006, the following therapeutic areas and drugs were on the priority list:

- Attention deficit/hyperactivity disorder: methylphenidate
- Hypertension: diuretics
- Parasitic diseases: albendazole, mebendazole
- Influenza: amantidine, rimantidine
- Cancer: methotrexate, daunomycin
- Poisonings: pralidoxime
- Sickle cell anemia: hydroxyurea

In March 2007, the following therapeutic areas, drugs, and research areas were on the priority list:

- Infectious diseases: methicillin-resistant *Staphylococcus aureus* infection: clindamycin, tetracyclines, trimethoprim-sulfamethoxazole
- Hypertension: clinical trial designs
- Neonatal research: clinical trial designs
- Cancer: neuroblastoma: 13-cis retinoic acid
- Asthma: clinical trial designs in young children.

From the priority list, NIH writes and negotiates a PPSR with FDA. FDA issues a WR to holders of the NDA or abbreviated NDA. If the holder accepts the WR, it conducts the study. If the holder declines, the study is referred to NIH for funding. NIH then publishes a request for proposals in FedBizOpps. To date, all requests to holders have been declined.

Ongoing BPCA studies and their status are as follows:
- Lorazepam—clinical studies of sedation of children on ventilators in an intensive care unit
- Lorazepam—clinical studies for treatment of status epilepticus
- Nitroprusside—clinical studies to reduce blood pressure during surgery to reduce blood loss
- Lithium—clinical studies to define treatment of mania in children with bipolar disorder
- Baclofen—clinical studies of oral baclofen to treat spasticity, most commonly from cerebral palsy
- Meropenem to treat serious intra-abdominal infections in infants
- Hydroxyurea to treat very young children with sickle cell disease
- Vincristine—studies to evaluate neurotoxicity, PK in children (in collaboration with the National Cancer Institute [NCI] and the Children's Oncology Group [COG])
- Actinomycin-D—studies to evaluate hepatotoxicity/veno-occlusive disease, PK in children (NCI-COG)
- Methotrexate—clinical studies to evaluate neurocognitive outcomes of pediatric patients with high-risk acute lymphoblastic leukemia (NCI-COG)
- Daunomycin—PK, safety, efficacy of daunomycin to treat childhood cancers and relationship to body weight (NCI-COG)
- Ketamine—preclinical studies to evaluate the scientific and safety concerns about the use as an anesthetic in children
- Methylphenidate—preclinical and clinical evaluation of PK and safety to understand reports of cytogenetic toxicity (NIEHS)
- Morphine—evaluations of the developmental and safety issues in treating pain in neonates.

Within the context of BPCA, the expected outcomes of the biodefense meeting are prioritization of therapeutic areas and various interventions and prioritization of drugs, biologics, devices, and needed studies for children and pregnant women. The studies should be specific and feasible.

Treatment of the Pregnant Patient
Mahmoud S. Ahmed, Ph.D., Professor, Department of Obstetrics and Gynecology, and Graduate Programs of Biochemistry, Molecular Biology, Pharmacology, and Toxicology, University of Texas Medical Branch, Galveston

The goal of Dr. Ahmed's research is to better understand the molecular mechanisms underlying human placental disposition of drugs used for therapy of the pregnant patient. Pregnancy is associated with physiological changes that affect the PK and pharmacodynamics (PD) of administered medications. The human placenta has a pivotal role during fetal organogenesis and development. The placenta performs numerous functions similar to those of other organs:
- Transfer of nutrients (like the GI tract)
- Exchange of gasses (like the lungs)
- Biotransformation of xenobiotics, environmental toxins, and therapeutic agents/drugs (like the liver)
- Release of hormones (like the autocrine and paracrine systems)
- Elimination of waste products (like the kidney)
- Functional barrier (neonatal abstinence syndrome).

In 1999, for studies of neonatal abstinence syndrome, Dr. Ahmed and colleagues hypothesized that the human placenta acts as a functional barrier that undergoes changes during pregnancy. The barrier is achieved by:

- Anatomical structure (permeability of compounds)
- Metabolic enzymes (anabolic and catabolic)
- Transporters (uptake and efflux)
- Genetic makeup and polymorphisms that affect activity of enzymes/transporters.

Drugs can affect fetal organogenesis and development in two ways:

- Directly—resulting from, and dependent on, concentration of the drug in the fetal circulation
- Indirect—resulting from the effects of the drug and/or its metabolites on the viability or functions of placental tissue.

Dr. Ahmed and colleagues have used a variety of techniques and methods in their research on placental transfer of therapeutic agents and drugs:

- Dual perfusion of placental lobule
- Placental subcellular fractions
- Short- and long-term villous tissue explant cultures (gestational age)
- Plasma membrane vesicles
- Genomics (molecular biology)
- Analytical (high-performance liquid chromatography, liquid chromatography–mass spectrometry, radioisotopes)
- Animal model (nonhuman primate).

The dual perfusion of placental lobules method has advantages and disadvantages:

Advantages	Disadvantages
- The use of hemomonochorial placenta - Investigations of the placenta as a barrier - Retention of anatomical and functional integrity (up to 24 hours) - Multiple samples from the maternal and fetal circuits	- Data obtained can not be extrapolated to earlier gestational age - Mechanical and or ischemic injury to the tissue - Lack of maternal and fetal metabolites that regulate placental functions - Drug access to metabolic enzymes less than *in vivo* - Success rate only 40 percent

The dual perfusion system allows the study of the kinetics of drug transfer; maternal, tissue, and fetal drug distribution; and effects of drug on tissue (viability and functional parameters).

Subcellular fractions of trophoblast tissue at different gestational ages can be used to identify placental drug biotransforming enzymes. Dr. Ahmed presented findings from biotransformation studies of the following:

- Methadone and buprenorphine (opiate addicts)
- Glyburide (gestational diabetes)

- 17-Hydroxyprogestrone caproate (preterm delivery)
- Bupropion (antidepressant/smoking cessation).

Dr. Ahmed also presented findings on studies of the following:
- Efflux transporters in an *ex vivo* assay for function
- P-glycoprotein (P-gp) expression during pregnancy
- Polymorphism of placental P-gp (MDR-1) gene
- Ethnic distribution of P-gp genotype variants
- Relative amounts of glyburide metabolites formed by human and baboon placental microsomes.

In conclusion, placental research allows a variety of studies for the treatment of the pregnant patient, including:
- Placental disposition of drugs
- PK/PD of drugs during pregnancy
- Differences in placental functions during gestation
- Pharmacogenetics (ethnicity and polymorphisms).

NIH Countermeasures Against Chemical Threats (CounterACT) Research Network
David A. Jett, Ph.D., Program Director for Counterterrorism Research, NINDS, NIH, HHS

The goal of the CounterACT Program is to develop novel therapeutic countermeasures or diagnostic technologies to enhance the nation's current medical response capabilities to a chemical incident.

There are differences in military and civilian challenges in preparedness to chemical threats:

Military Focus	Civilian Focus
- War fighter: 18–45 years old and healthy - Open air environment - High number of casualties is the goal - Prophylactic measures are the focus	- Broad age range: pediatric–elderly - May have preexisting medical conditions - Could happen in closed environment - No need for high casualties - Postexposure therapies are the primary focus - First responders and decontamination personnel

Historical milestones for the CounterACT Program are as follows:
- Fiscal year (FY) 2002—Department of Defense contacted NINDS to initiate collaborations
- FY 2003—NINDS launched Supplement Program
- FY 2004—NIAID Workshop on Chemical Threats; NINDS Workshop on Nervous System Threats
- FY 2005—President's FY 2006 budget includes funds for chemical threats; Anticonvulsant Expert Panel; Cyanide Expert Panel; Pulmonary Agents Expert Panel

- FY 2006—NIAID convened Blue Ribbon Panel on Chemical Threats; five solicitations for research application published; centers, projects, Small Business Innovation Research grants (SBIRs), contracts, and interagency agreements funded
- FY 2007—First Annual CounterACT Meeting; NIAID convened Blue Ribbon Panel on Toxic Vesicants
- FY 2008—Released two additional requests for applications; Second Annual CounterACT Meeting.

NIH ICs collaborating on the CounterACT Program include:
- NIAID
- NICHD
- NINDS
- NIEHS
- NIAMS
- National Institute of General Medical Sciences
- National Eye Institute.

The scope of the CounterACT Program's research is broad. It includes:
- Basic/fundamental research
  - Mechanistic studies—target identification (therapeutic/diagnostic)
  - Standardized models—*in vitro* and *in vivo* models for efficacy screening
- Advanced/translational research
  - Medicinal chemistry optimization
    - Physical/chemical reformulations to prolong "shelf-life"
    - Alternate route of administration (safe, effective, easy, and rapid)
- Preclinical Investigational New Drug (IND) development
  - Absorption, distribution, metabolism, and excretion; toxicology/developmental chemistry
  - Current Good Laboratory Practices (GLP)
- Phase 1 clinical trials—NINDS Neurological Emergencies Treatment Trials (NETT)
- Preclinical development facility
  - Advanced preclinical development of promising candidate medical countermeasures
  - Safety, toxicology, PK/PD, tissue distribution, and chemistry and manufacturing studies for candidate drugs in partial fulfillment of the requirements for submitting an IND application to FDA
- Anticonvulsant screening program
  - High throughput screening using established and new models
  - Anticonvulsants plus neuroprotectants.

The CounterACT Research Network is composed of research projects, research centers, small business innovation research, and contracts. The FY 2008 CounterACT portfolio is 64 percent academia (28 centers), 18 percent industry (9 centers), and 18 percent government (9 centers). Within the portfolio, there are six research centers of excellence, six SBIRs, two contracts (ASP and SRI), four interagency agreements, and 31 research projects, including one clinical trial.

The areas of research for chemical targets are as follows:
- Respiratory tract (chlorine, ammonia, etc.)—16 percent
- Cellular respiration (cyanide)—10 percent
- Diagnostic technology (organophosphate [OP] detectors, electroencephalographs, etc.)—16 percent
- Nervous system (OP chemical warfare agents, neurotoxins, etc.)—48 percent
- Skin, eyes, mucous membranes (sulfur mustard, 2-chloroethyl ethyl sulphide, etc.)—10 percent.

NIH/NINDS clinical expertise is being applied to a number of trials:
- NETT
  - Nationwide network (17 Hub institutions with 3 Spoke hospitals each)
  - Long-term resource; does not end with completion of one study
    - High-Dose Albumin Therapy for Neuroprotection in Acute Ischemic Stroke (ALIAS)
    - Progesterone for Traumatic Brain Injury: Experimental Clinical Treatment (ProTECT)
    - Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPArT)
- RAMPArT
  - Prehospital phase 2/3 trial with IM midazolam in seizure patients
  - Noninferiority IM midazolam versus IV lorazepam
  - Exception from informed consent for emergency research
- Coordinated and in collaboration with Department of Defense (DoD) phase 1 trials and definitive animal studies with nerve agent.

There are several elements of NIH–DoD biodefense collaboration:

NIH	DoD
- Animal Rule definitive GLP studies at Battelle (in progress)	- Animal proof-of-concept studies (completed)
- Submit IND for RAMPArT	- IND submitted for NDA
- RAMPArT (in preparation)	- Phase 1
- NDA for status epilepticus	- Contract of filled autoinjectors (completed)
	- NDA label to include military and civilian use

Biodefense and Public Health Threats: Now and into the Future
Michael G. Kurilla, M.D., Ph.D., Director, Office of Biodefense Research Affairs, Division of Microbiology and Infectious Diseases; Associate Director, Biodefense Product Development, NIAID, NIH, HHS

Despite historical predictions of the eradication of infectious diseases, infectious agents—intentional and unintentional—continue to pose threats to public health. There are newly emerging, reemerging, and "deliberately emerging" threats of natural and bioterrorist origin. Natural threats include sudden acute respiratory syndrome (SARS), avian flu, Lyme disease,

methicillin-resistant *Staphylococcus aureus*, West Nile virus, and multidrug-resistant tuberculosis. Bioterrorist threats include anthrax, smallpox, and Ebola virus.

NIAID's infectious disease research has a dual mandate: (1) maintain and "grow" a robust basic and applied research portfolio in microbiology, immunology, and clinical research; and (2) respond rapidly to new infectious disease threats. However, the tension between "supply" and "demand" has led to market failure. NIH-sponsored research generates new concepts that lead to innovative interventions, but the provider of acquisition funding is responsive to commercial interests and concerns.

Aspects of NIAID's countermeasure research and development include vaccines, therapeutics, diagnostics, genomics, basic research, clinical research, and expansion of research capacity. NIAID is part of PHEMCE. The PHEMCE implementation plan includes countermeasures against anthrax, smallpox, botulism, hemorrhagic fever viruses (HFV), plague, tularemia, and other bacterial threats. The status of progress to date is as follows:
- Second generation anthrax vaccine (recombinant protective antigen [rPA])
  – Two successful phase 2 trials completed
  – Acquisition contract under review
- Next-generation smallpox vaccine (modified vaccinia Ankara [MVA])
  – Potential vaccine platform
  – Acquired by HHS for the SNS
- Enhanced, more potent botulism therapy
  – Heptavalent version delivered to SNS (has already been used)
  – Monoclonal antibodies ready for clinical trials
- HFV
  – Multivalent vaccine effort being initiated
  – Novel technology developing therapeutic interventions.

To improve on this progress, NIAID's biodefense strategy is to build on PHEMCE and Homeland Security Presidential Directive 18. NIAID's efforts will focus on (1) traditional, enhanced, emerging, and advanced agents; and (2) Tier I and II defense strategies. A comprehensive solution will require a change in perspective. There are multiple elements to NIAID's flexible approaches.

There are broad spectrum approaches such as:
- Activity (products)
  – Products applicable to classes of threats
  – Host-directed interventions
  – Immunomodulators
- Technology (product enhancements)
  – Temperature stabilization
  – Alternative delivery devices
  – Vaccine adjuvants
- Platforms (production)—standardized manufacturing systems (another egg).

There are cutting-edge technologies that include:
- Host protein identification
- Novel technical approaches (for example, use of random homozygous knock-out [RHKO])
- Targets include pathways for entry, egress, assembly, and intracellular maintenance.

New research is targeting viral entry pathways:
- Basic entry mechanism
  - Glycoprotein attachment
  - Endosomal uptake
  - pH-mediated proteolytic activation
  - Membrane fusion
- Target—host cysteine proteases
- Agents—Ebola, SARS, and Nipah virus.

New research is focusing on aspects of viral egress such as TSG101—an intracellular protein appearing on the surface during viral egress. This protein is involved with Ebola, HIV, and influenza (and perhaps all enveloped viruses). Another focus is monoclonal antibodies that freeze viruses and cells in a nonproductive state.

Another targeted research area is viral assembly. There is a new paradigm that viral capsid assembly is a catalyzed process. One company has identified small molecules that interfere with this process for nearly every viral family (most advanced candidate has 100-percent efficacy in murine Ebola infection). This approach offers potential for identifying treatments before etiologic agents are identified.

Progress in intracellular maintenance research includes development of Gleevec—a cancer drug that targets Abl family tyrosine kinases. Gleevec is active against orthopoxviruses by inhibiting host kinase function. Recent work suggests that intracellular bacteria use a similar pathway.

Future NIAID countermeasure research and development will focus on the following:
- Vaccines
  - Nonneedle delivery
  - Long-term stabilization
  - Multivalency (cross-protection)
  - Faster induction
  - Adjuvants (rationale design and selection)
- Therapeutics
  - True broad spectrum
  - Innate immune augmentation
  - Host-based directed interventions
- Diagnostics
  - Multiplexed adaptive platforms
  - Rapid proof of concept; clinical decision-making impact
  - Host-based systems.

Systems for Preparedness and Response: Countermeasure Development to Dispensing

Richard Besser, M.D., Director, Coordinating Office for Terrorism Preparedness and Emergency Response, CDC

The American public faces a variety of urgent threats:
- Infectious diseases such as West Nile virus, SARS, food-borne disease (for example, Salmonella), and pandemic flu
- Terrorism events (for example, 9/11 and anthrax)
- Natural disasters such as wildfires, hurricanes, and floods.

Public health preparedness is the continuous process of improving the health system's capacity to detect, respond to, recover from, and mitigate the consequences of terrorism, health emergencies, and other urgent threats. The goal of public health preparedness is to protect people in all communities from infectious, occupational, environmental, and terrorist threats. The SNS plays a vital role in meeting this goal. PHEMCE also plays a vital role by coordinating the following agencies and their respective roles and responsibilities:
- NIH—research and development (the science)
- BARDA—advanced development
- BARDA and CDC—acquisition
- CDC—storage and maintenance
- CDC and the Office of Preparedness and Emergency Operations—deployment and use.

Aspects of the science include:
- Epidemiology
  - Medical consequences modeling
  - PHEMCE integrated program teams
- Laboratory science—agent specific assay development
- Countermeasure development
  - Anthrax immune globulin
  - Anthrax vaccine research program
- Pharmacology—agent formulation and storage.

Aspects of acquisition and storage include:
- Mission—getting the right product to the right place at the right time
- National repository of antibiotics, antivirals, chemical antidotes, antitoxins, life-support medications, and medical supplies
- Funding and managing complex activities to acquire, store, and appropriately place countermeasures
  - Procurement
  - Storage
  - Packaging
  - Sustainment, including shelf life extension
  - Security.

The goals of deployment are to provide (1) threat-appropriate delivery mechanism, (2) rapid delivery of a broad spectrum of support for an ill-defined threat in the early hours of an event (Push Packages), and (3) large shipments of specific materiel when a threat is known.

The goal of distribution and dispensing is to provide ongoing technical assistance to state and local public health organizations to help them develop capacity for countermeasure distribution. Programs and projects include:
- Public Health Emergency Preparedness Program
- Cities Readiness Initiative
- MedKit Project
- Private-sector engagement
- Point-of-dispensing (POD) drills and exercises
- Satellite broadcasts.

The Public Health Emergency Preparedness Cooperative Agreement:
- Provides guidance and funds to state and local public health entities to strengthen preparedness and response
- Develops systems to prevent, detect, investigate, respond to, and recover from emergencies
- Develops performance metrics and gathers performance data on exercises and real events through state reporting
- Provides technical assistance to move materiel from warehouses to points of dispensing.

The Cities Readiness Initiative:
- Provides mass prophylaxis to 100 percent of the identified population within 48 hours of the decision to do so
- Strengthens preparedness capabilities of largely populated U.S. cities and their Metropolitan Statistical Areas (MSAs)
- Decreases the time it takes to dispense prophylaxis by increasing POD throughput and offering alternate modalities of dispensing, such as postal service option, predeployed community caches, preevent dispensing to first responders, and private-sector partnerships.

In 2007, CDC's Division of Strategic National Stockpile conducted the Emergency MedKit Evaluation Study. The overarching aim of the MedKit Project was to evaluate a strategy that addresses the timeliness of distributing antibiotics to the general public as an effective measure against a release of anthrax. Part of the MedKit Project was a pilot study to test the feasibility of preevent placement of caches of antibiotics in households. Participants included 4,250 households in the St. Louis MSA. More than 95 percent of households followed instructions on proper storage, maintenance, and the use of antibiotics. More than 90 percent of the households reported that they would like to have MedKit in the home.

With regard to planning and response considerations for children, the National Advisory Committee on Children and Terrorism made recommendations to the Secretary of HHS in 2004. The SNS has implemented most of the recommendations even with no additional funding provided to address them. Pediatric-specific containers were created within the 12-hour Push Packages. The SNS now contains pediatric sizes of the following:

- Aerosol masks/nebulizers
- Non-rebreather masks
- IV ancillary supplies
- Ventilators and associated ancillary supplies
- Endotracheal tubes, stylettes, laryngoscopes
- Suction catheters
- OP airways
- Ambu-bags
- Nasogastric tubes
- Oral dosing syringes
- Broselow tapes
- Weight-based dosing of IV medications

In addition, pediatric atropens are now included in CHEMPACKs. Other aspects of planning and response considerations for children include:
- Age cut-off for suspensions raised to age 9 and younger
- Pediatric suspensions for amoxicillin, doxycycline, and ciprofloxacin
- CDC worked with FDA to develop easy-to-follow tablet crushing guidelines for doxycycline home preparation (if suspensions run out)—posted on FDA Web site
- Pediatric dosage forms of oseltamivir
- Liquid KI (potassium iodide oral solution) procured through Project BioShield
- CDC is creating pre-Emergency Use Authorization documents for Prussian blue in children younger than 2 years of age (for internal cesium-137 contamination) and for midazolam (for seizures related to chemical nerve agent exposure)
- All procurements of countermeasures for the SNS under Project BioShield provide options to study and potentially license the countermeasures for pediatric patients.

Challenges remain. An ever-growing percentage of the SNS budget is consumed by storing, maintaining, and replacing the countermeasure inventory. Lifecycle costs are a significant part of any acquisition. Countermeasures are of no value if they cannot be dispensed in an appropriate timeframe. Measurement of this capability is an ongoing challenge. Meeting the needs of children is critically important. Shortage of FDA-approved products is a major challenge.

Immunity to Anthrax with Special Emphasis on Infants and Children
John Robbins, M.D., Co-Director, Program on Developmental and Molecular Immunity, NICHD, NIH, HHS

Anthrax is an infectious disease of wild and domesticated animals, especially cattle and sheep, that is caused by a bacillus (*Bacillus anthracis*) and can be transmitted to man. Anthrax infection is characterized by black pustules. The anthrax bacillus is an encapsulated, gram-positive bacteria. It was the first bacterium shown to be the cause of a disease. In 1877, Robert Koch grew the organism in pure culture, demonstrated its ability to form endospores, and produced experimental anthrax by injecting it into animals. French scientist Louis Pasteur developed the first effective vaccine for anthrax in 1881.

In 1925, the first large-scale use of anthrax vaccine in cattle began in South Africa. By 1941, the active immunization against anthrax in cattle was proven to be effective in reducing the number of outbreaks and the number of deaths. In 1946, protective antigen (PA) from cell-free culture filtrates was developed. The PA was shown to confer immunity to anthrax in rabbits. A

subsequent study of alum-precipitated PA showed its immunizing activity to intracutaneous anthrax in rabbits and monkeys. The study was published in 1954.

The human vaccine for anthrax became available in 1954. This was a cell-free vaccine instead of the live-cell Pasteur-style vaccine used for veterinary purposes. Field evaluations of a human anthrax vaccine (anthrax vaccine adsorbed [AVA]) began in 1962. The field evaluations were conducted in wool sorters in Manchester, NH. AVA was shown to be an effected vaccination in the wool sorters. The vaccine was produced from one nonvirulent strain of the anthrax bacterium. Between 1962 and 1974, CDC continued to study the vaccine in the Manchester area and confirmed the vaccine's efficacy to cutaneous anthrax. An improved cell-free vaccine became available in 1970.

AVA has its limitations. The protective moiety in the vaccine cannot be measured directly. Consistency of production is difficult to maintain because there is no precise standardization for lot release. There is no direct measure of the PA in the vaccine. Besides PA, AVA contains other components that cause adventitious reactions. AVA elicits a relatively high rate of local and systemic reactions that provoked criticism of anthrax vaccination in the military and much inaccurate information about its safety. This inaccurate information has resulted in difficulty in recruiting adult volunteers for investigational anthrax vaccines. The local and systemic reactions do not cause permanent injury. The schedule for subcutaneous injections of AVA to the armed forces—0, 2, and 4 weeks and 6, 12, and 18 months with subsequent yearly boosters—was introduced in the 1950s. The 2-week interval between the first three injections was designed for rapid induction of immunity in individuals at risk. The injections at 6, 12, and 18 months were not founded on published protocols. There is no information about the safety, immunogenicity, or efficacy of AVA in children.

Studies of human antibody kinetics after anthrax vaccination have revealed that adults have a small amount of preexposure antibody. There are no antibody-free adults. Studies of U.S. military personnel have shown that they are all partially immune prior to vaccination.

In a 2004 study of mice, researchers identified anthrax toxin genes in a *Bacillus cereus* associated with an illness resembling inhalation anthrax. A literature review in 2006 indicated that the anthrax toxin is a common finding among many enteric organisms. Proteins related to the "protective antigen" of *Bacillus anthracis* have been found in a number of bacteria, including *Clostridium perfringens, Clostridium spiroforme, Clostridium difficile, Clostridium botulinum, Bacillus thuringiensis,* and several strains of *Bacillus cereus.* These organisms do not cause an acute antibody response. Humans respond with low-level, natural antibody formation. In many instances, adults become partially immune to anthrax. Certain biochemical aspects of the anthrax spore and capsule are found in other bacteria. These aspects are believed to be involved in the cross-reactivity of the organisms and the resulting partial immunity in adults. The results of many studies indicate that immunoprotection can be conferred without prior exposure to a pathogen.

In conclusion, almost nothing is known about immunity to anthrax in infants and young children. There are very few quantitative data in the literature. There is a community misperception that

anthrax vaccines are dangerous; they are not. The licensed vaccine causes local and systemic reactions but does not cause permanent injury. Researchers should focus on multiantigen vaccine approaches to enhance the protective response to vaccination. Multiantigen approaches include PA, poly-gamma-D-glutamic acid, and anthrose conjugates.

Overview of Research: NIAID Radiation/Nuclear Program

Andrea L. DiCarlo-Cohen, Ph.D., Program Officer, Radiation/Nuclear Countermeasures Group, NIAID, NIH

Radiological and nuclear threats come from a variety of sources:
- Nuclear detonation
- Radiological dispersive devices ("dirty bombs")
- Radiological exposure devices (concealed source)
- Industrial and shipping accidents—power plant releases, food and medical irradiators, sealed sources.

There is a spectrum of radiation health effects that depend on the dose of exposure. Survival is possible with mild-to-moderate exposures (0.5–3.5 grays [Gy]). Higher exposures increase the risk of death. Exposures of 7.5 Gy and greater lead to certain death.

There are a number of opportunities for new medical countermeasures for radiological and nuclear incidents:
- Preexposure protectants including amifostine, phosphenol, vitamin E, and genistein
- Radiation exposure assessments such as cytogenetic assays, dosimetry, and biomarkers
- Postexposure therapeutics including G-CSF and cytokines, antimicrobials, and immune system recovery.

Radiation syndromes manifest over time. Within days or weeks after irradiation, bone marrow, skin, GI, or combined injuries become apparent. Lung and kidney injuries appear months after exposure. Organ dysfunction may occur years later. Secondary malignancies may appear decades later.

The research goals of radiological/nuclear countermeasures include:
- Immediate
  - Facilitate label expansion for licensed drugs and their addition to the SNS
  - Develop Centers for Medical Countermeasures Against Radiation (CMCRs)
- Intermediate/long-term
  - Develop broadly acting safe and effective radioprotectants and therapeutic drugs
  - Develop biodosimetry tools and bioassays to evaluate radiation injury
  - Address critical gaps in understanding mechanisms leading to injury induced by ionizing radiation
  - Support stem cell research effort toward reconstitution of the immune system following radiation-induced injury.

There are four components to NIAID's Radiation/Nuclear Countermeasures Group mission:
- Acute Radiation Syndrome/Delayed Effects of Acute Radiation Exposure (ARS/DEARE)
- Radiation combined injury
- Radionuclide injury
- Biodosimetry (triage and predictive).

The Radiation/Nuclear Program has provided 65 awards for research capitalizing on existing products, SBIRs, product development, and regulatory support. Focused funding areas include:
- Oral DTPA
- Immune reconstitution
- Novel decorporation agents
- GI dysfunction
- Combined injury
- Thrombocytopenia
- Skin damage
- Lung late effects.

Countermeasures of special interest include:
- Statins (atorvastatin, simvastatin)
- Somatostatins (octreotide [Sandostatin], SOM230)
- Angiotensin converting enzyme (ACE) inhibitors (ramipril, captopril)
- Angiotensin receptor blockers (losartan)
- Growth factors (G-CSF, GM-CSF, KGF, HGH)
- Manganese superoxide dismutase (MnSOD) mimetics (Euk compounds)
- Toll-like receptor agonists (CBLB502)
- Nutraceuticals (genistein, curcumin, vitamins E and C)
- Platelet-enhancing factors (thrombopoietin [TPO] receptor agonists)
- Others (pentoxifylline, cell therapies).

The product development support contract includes:
- Screening and evaluation of drug candidates—hematopoietic ARS, GI ARS
- Good Manufacturing Practices manufacturing
- GLP nonclinical toxicology and safety testing
- GLP pivotal animal efficacy studies
- FDA animal rule—nonhuman primates, rodents
- Human phase 1 safety studies
- New facilities.

Thrombocytopenia treatment challenges include:
- Current therapy after exposure is transfusion—challenge in mass casualty
- Government needs effective countermeasures
- PEG-MGDF—autoantibody formation in humans, TPO removed from market
- Second generation TPO drugs (species specificities)
  - Romiplostim—recently licensed for idiopathic thrombocytopenic purpura (ITP)
  - PEG-TPO mp

– Eltrombopag oral, nonpeptide, FDA review for ITP.

Pediatric radiation research focuses on:
- Animal model development (FDA animal rule)
    – Pregnant mothers and *in utero* exposure
    – Infants, juveniles and teens
- Mining of existing databases (atomic bombings, nuclear accidents)
- Pediatric dosing for existing and novel countermeasures
- Establishing gold standard biodosimetry.

Pediatric biodosimetry efforts in the Radiation/Nuclear Program are focusing on:
- Ensuring that early induction of lung inflammatory markers seen in adults postradiation will not occur during postnatal lung development
- C57Bl/6 mice
    – Adult (6–8 weeks), whole lung or total body irradiation (0–10 Gy) or juvenile C57Bl/6 pups, 4–56 days, total body irradiation (5 Gy)
    – Cytokine mRNA, protein expression (lung, liver, serum)
    – TUNEL staining for lung damage.

Pediatric late effects studies are focusing on:
- Coronary sclerosis, structural and functional cardiac degeneration in adult rats exposed to radiation as juveniles
    – Total body irradiation (10 Gy) at (35 days of age)
    – Evaluate cholesterol, triglycerides, and C-reactive protein
    – Liver injury
    – Heart structure, function, and injury
    – Morphological, functional, and molecular biology studies
- Study of captopril, losartan, erythropoietin, 5-AED, pravastatin, simvastatin, and curcumin.

Future pediatric program plans will emphasize the need to address special populations in grant applications. The program mandate is to focus on new formulations of novel or existing products that can be easily administered to all civilian populations, including infants, children, the elderly, and the chronically ill. Program plans include developing animal models, exploring how to do phase 1 safety studies, and providing expertise.

OPPB Biodefense Working Groups

Three OPPB biodefense working groups were formed to:
- Discuss issues related to current biodefense countermeasures for children and pregnant women
- Review ongoing animal studies and adult clinical studies
- Identify gaps in medical countermeasures, therapeutic agents, and devices
- Make recommendations to guide research and clinical studies.

The working groups are composed of representatives from academia, federal agencies, and the private sector. Group members include acute care clinicians, toxicologists, pharmacologists, and oncologists. Participating federal agencies include NIAID, NICHD, NINDS, NIEHS, NIAMS, NLM, NCI, FDA, and CDC.

The OPPB biodefense working groups and subgroups are as follows:
- Chemical Working Group
  - Cyanide Subgroup
  - Nerve Agents Subgroup
  - Pulmonary Agents Subgroup
- Infectious Disease Working Group
  - Vaccines Subgroup
  - Antibiotics, Antivirals, and Antitoxins Subgroup
- Radiation Working Group.

During the meeting, each working group or subgroup was asked to review its respective area or areas of interest and report its findings and recommendations. The working groups or subgroups were asked to complete a review outline and set priorities for therapeutic areas and therapeutic agent or device.

Chemical Working Group Report

Cyanide. Cyanide interrupts respiration in the mitochondrial electron transport chain. Traditional treatment approaches have been to draw cyanide out of mitochondria by its affinity for the heme iron in methemoglobin. Initially, a nitrite is infused to cause a modest 15–20 percent degree of methemoglobinemia and to pull cyanide off the electron transport chain in mitochondria and convert it with the endogenous enzyme rhodanase to the much less toxic chemical thiocyanate.

Traditional treatment of cyanide poisoning involves a two-step process: administration of amyl or sodium nitrite followed by administration of sodium thiosulfate. In a mass casualty scenario, there are issues with administering the traditional antidotes amyl nitrite and sodium nitrite: (1) the degree of methemoglobinemia can be exceeded, which is critical in pediatric treatment, and (2) because the nitrites are vasodilators, hypotension may be induced. A new antidote—hydroxocobalamin (HC)—does not have these issues. HC is used extensively in Europe and by emergency medical services (EMS) in the United States. It is approved by FDA as an antidote for cyanide toxicity.

The Cyanide Subgroup reported the following:
- Biodefense therapeutic area: Cyanide
- Biodefense therapeutic agent/device: HC and cobinamide
- Biodefense clinical need: To identify appropriate pediatric dose
- Nonbiodefense clinical need(s): To obtain more pediatric data, for example, by contacting appropriate agents in France, where HC is being given regularly to children
- Current FDA-approved indications and dosing:
  - Adults: 5 gm IV

- – Pediatric dose: none is FDA-approved but label states that 70 mg/kg has been given to children
  - – In Europe, recommended dose is 70 mg/kg with a maximum of 140 mg/kg
- Current FDA-authorized age groups: Adults only
- Current available formulations/shelf life: Little available information
- Current off-label use and dosing: Little available information
- Route of administration/monitoring:
  - – Need more sensitive method for measuring cyanide in blood
  - – New technology may be available soon
  - – Need to explore more routes of administration, for example, IM
  - – Need to explore safety of different concentrations
- Needed studies for biodefense clinical indication:
  - – Pediatric studies of HC
  - – Studies of HC in lactating women
- Needed studies for nonbiodefense clinical indications:
  - – Studies in the use of HC in patients receiving nitroprusside
  - – Studies of pediatric fire victims
    - – HC versus cyanide antidote kit
    - – Need more sensitive measure of blood cyanide
    - – Consider three-arm trial (one group receives all)
  - – Studies of HC without sodium thiosulfate
- Relevant ongoing clinical trials: Ongoing cobinamide studies
  - – What is the timeline for cobinamide development versus the timeline for conducting HC studies in children to obtain FDA approval?
- Ethical concerns: May require input from EMS community.

Nerve Agents. The traditional therapeutic approach for nerve agents is a combination of an anticholinergic agent—most commonly atropine—with a substance from the oxime class of chemicals. The standard treatment is the atropine autoinjector. The Nerve Agents Subgroup reported the following for scopolamine:
- Biodefense therapeutic area: Nerve agents
- Biodefense therapeutic agent/device: Scopolamine
- Biodefense clinical need: Testing against atropine; scopolamine may have better CNS penetration with a lower profile of severe side effects
- Nonbiodefense clinical need(s): Better treatment for organophosphates?
- Current FDA-approved indications and dosing: Treatment of nausea, motion sickness, and intestinal cramping; some use in postoperative pediatric critical care
- Current FDA-authorized age groups: Children and adults
- Current available formulations/shelf life: IM, IV, subcutaneous, transdermal
- Mechanism of action, available age-related PK data: Requires further exploration
- Route of administration/monitoring: IM, IV, tablet, patch, or Canadian preparation
- Needed studies for biodefense clinical indication: Atropine plus pralidoxime with scopolamine add-on
- Needed studies for nonbiodefense clinical indications: Developing country; find/join a research group, methodology to be identified

- Relevant ongoing clinical trials: Studies of organophosphate poisoning/toxicity in Southeast Asia and Australia
- Ethical concerns: Resolve ethical issues.

The Nerve Agents Subgroup reported the following for the pralidoxime pediatric autoinjector:
- Biodefense therapeutic area: Nerve agents
- Biodefense therapeutic agent/device: Pralidoxime pediatric autoinjector (2PAMCI)
- Nonbiodefense therapeutic area: IV for pesticide poisoning, children and adults
- Current FDA-approved indications and dosing: 600-ml autoinjectors; FDA is reviewing pediatric data, but timing for approval of 2PAMCI is still unknown
- Current FDA-authorized age groups: Adults
- Mechanism of action, available age-related PK data: Even adult data are deficient and inconsistent
- Route of administration/monitoring: IM, IV
- Recommendation: Develop a pediatric size autoinjector and appropriate dosing.

Death from exposure to nerve agents is generally due to intractable seizures (that is, seizures that do not respond to conventional treatment agents). Uncontrolled seizures end in death or permanent neurologic disability. Therefore, the focus of nerve agent treatment should be neuroprotection and agents that offer neuroprotection and better outcomes. The Nerve Agents Subgroup reported the following for midazolam:
- Biodefense therapeutic area: Nerve agents
- Biodefense therapeutic agent/device: Midazolam; enters CNS faster than other benzodiazepines such as Valium and Ativan
- Biodefense clinical need: Gather data for a pediatric labeling application for treatment of refractory seizures
- Nonbiodefense clinical need(s): Treatment of organophosphate/pesticide poisoning, treatment of pediatric seizures
- Current FDA-approved indications and dosing: Seizures not on the list
- Current FDA-authorized age groups: Children and adults
- Mechanism of action, available age-related PK data: Extensive data available
- Route of administration/monitoring: IM, IV, nasal, buccal
- Recommendation: Sufficient data to support immediate use of midazolam; can and should be used to treat nerve agent exposure; should be made immediately available in the SNS and CHEMPACKs as a nerve agent treatment.

Reactive Skin Decontamination Lotion (RSDL) is a patented, broad-spectrum liquid decontamination lotion intended to remove or neutralize chemical warfare agents or T-2 fungal toxin from the skin. It is FDA-approved for use by U.S. military and prehospital health care personnel. RSDL must be applied to exposed skin as soon as possible after exposure to a chemical agent. When exposed to chemical warfare agents, the user wipes the exposed skin with the lotion. The lotion removes the agents or the T-2 toxin and reacts with the chemical agents, rapidly neutralizing them so they are nontoxic. FDA cleared the lotion for use based on studies conducted by the U.S. Department of the Army that showed it is safe and effective. The Army tested the product's safety by conducting skin irritation, sensitization and photo irritation studies

in more than 300 people. It tested its effectiveness by using it to treat animals that had been exposed to chemical agents. The Nerve Agents Subgroup reported the following for RSDL:
- Biodefense therapeutic area: Nerve agents
- Biodefense therapeutic agent/device: RSDL
- Biodefense clinical need: Mass casualty incident, immediate treatment in the field
- Nonbiodefense clinical need(s): Organophosphate/pesticide poisoning
- Current FDA-approved indications and dosing: Removal/neutralization of chemical warfare agents and T-2 fungal toxin
- Current FDA-authorized age groups: Adults.

The Nerve Agents Subgroup recommended that (1) the requirements for use of RSDL to treat children in a mass casualty situation be determined and (2) RSDL be made available to treat children if it is safe and effective.

The Nerve Agents Subgroup reported the following for ketamine:
- Biodefense therapeutic area: Nerve agents
- Biodefense therapeutic agent/device: Ketamine
- Biodefense clinical need: Second-line agent for organophosphate-induced refractory status epilepticus
- Nonbiodefense clinical need(s): Nonspecific neuroprotection from seizures
- Current FDA-approved indications and dosing: Procedural sedation, general anesthesia, analgesia; used in more than 15,000 U.S. children per year in emergency departments
- Current FDA-authorized age groups: Adults
- Mechanism of action, available age-related PK data: much human data available; recent animal data suggest ketamine neuroprotection against refractory seizures; was part of successful rabies treatment regimen in single human case
- Route of administration/monitoring: IV, IM, orally
- Needed studies for biodefense clinical indication: Potential neuroprotectant against nerve agent-induced refractory seizures
- Needed studies for nonbiodefense clinical indications: Potential neuroprotectant against organophosphate/pesticide-induced refractory seizures
- Relevant ongoing clinical trials: None
- Ethical concerns: Possible neurotoxicity in children younger than 1 year.

Pulmonary Agents. The primary pulmonary agents are chlorine, phosgene, and mustards. All of the agents are bronchial irritants causing significant reaction in the airways, including airway edema and reactive airway dysfunction syndrome. Course of treatment depends on the pulmonary agent. Because chlorine is water soluble, it has an immediate impact on the upper respiratory system. Because phosgene is less water soluble, it goes deeper into the respiratory system. Fluid may develop in the lungs within 2–6 hours. Other effects may appear up to 48 hours after exposure. Treatment focuses on acute lung injury.

The Pulmonary Agents Subgroup reported the following:
- Biodefense therapeutic area: Pulmonary agents

- Biodefense therapeutic agent/device: N-acetylcysteine, aminophylline, isoproterenol, ibuprofen, nebulized bicarbonate, surfactants, steroids, and others
- Biodefense clinical need: Prevention of pulmonary agent toxicity
- Nonbiodefense clinical need(s): Treatment of asthma, bronchiolitis
- Needed studies for nonbiodefense clinical indications: Bronchiolitis; animal studies of standardized exposure; systematic data collection in the event of a disaster; use of a systematic treatment approach
  - Primate studies
    - Will produce more information on ventilation
    - Will produce more information on respiratory failure
    - Will permit exploration of 3-chlorotyrosine
  - Prospective, acute human studies
- Ethical concerns:
  - Informed consent for data collection in disaster/mass casualty situation
  - Central institutional review boards (IRBs)
  - How to conduct multicenter studies
    - Poison centers
    - Pediatric Emergency Care Applied Research Network
    - Hospital consortia.

Infectious Disease Working Group Report

Vaccines. The Vaccines Subgroup reported the following for currently deployed anthrax vaccines:
- Biodefense therapeutic area: Anthrax
- Vaccine description: AVA
- Evidence for biodefense clinical need: One known attack and weaponized spores
- Nonbiodefense clinical need(s): Regions with endemic infections, potential clinical trial sites
- Current FDA-approved or Emergency Use Authorization (EUA) indications: Yes to both
- Administration requirements/dosing:
  - Licensed preparation has 6–8 doses about 1 month apart; developed for workers in textile plant
  - May get short-term protection from three doses
- Route of administration/monitoring: Subcutaneous, IM
- Is postexposure administration projected to have benefit?
  - Yes. Antibiotics and vaccine are beneficial.
  - Interval between exposure and disease may be long (up to 60 days).
- Current FDA or EUA authorized age groups:
  - Approved for pregnant women; antibiotics with vaccine following pregnancy
  - Experience in children younger than 18 years: No
  - Dose response in different age groups: Not known
- Current available formulations/shelf life: Anthrax culture supernatant adsorbed to alum and treated with formalin; 3 years
- Adverse events (short-term) associated with vaccine administration:
  - Fever attributable to vaccine, low grade, 5 percent, not likely to interfere with pregnancy

- Local reactions (swelling, inflammation), pain common
- Adverse events (long-term) associated with the vaccine:
  - Any reasons to suspect the consequences would be different in children? No
  - Any reasons to suspect the consequences would be different in pregnant women? No
- Relevant current ongoing clinical trials: Dosage reduction and IM administration route to simplify schedule and reduce side effects
- Ethical concerns: Testing vaccine in children without risk for infection (for example, children in the United States); consider locations with endemic infection; young sheep/goat herders
- What are the conditions for emergency use in persons younger than 18 years and in pregnant women? In event of exposure or threat, antibiotics and vaccine
- Recommended "next step":
  - Epidemiological information describing feasibility of studies in endemic areas
  - Develop protocol for safety and immunogenicity evaluation following postexposure use in children.

The Vaccines Subgroup reported the following for new anthrax vaccines undergoing studies:
- Biodefense therapeutic area: Anthrax
- Vaccine description: rPA, in clinical development, FDA considering, need phase 3 studies, may move into SNS
- Evidence for biodefense clinical need: Use of weaponized spores
- Nonbiodefense clinical need(s): Areas endemic for anthrax
- Administration requirements/dosing:
  - Three-dose schedule, 0, 2, 4 weeks in event of postexposure use
  - Preexposure use similar to AVA
- Is postexposure administration projected to have benefit? Yes
- Status of current clinical trials:
  - Does the dose response in different age groups vary (including children)? Definitely need trials in place to evaluate dose and schedule
  - Provide data, antibody measurements available from dose-response studies in young adults
  - Is there any experience in pregnant women? Not with rPA
- Adverse events (short-term) associated with vaccine administration: Thought to be better tolerated than licensed product, local reactions may be less
- Adverse events (long-term) associated with the vaccine:
  - Any reasons to suspect the consequences would be different in children? No
  - Any reasons to suspect the consequences would be different in pregnant women? No
- Relevant ongoing clinical trials, designated new trials:
  - New adjuvants need to be tested (for example, CpG)
  - Adjuvants tested in animal models
  - Preclinical evaluation of capsule or spore antigens improve immunogenicity
- Needed additional studies for children and pregnant women for biodefense clinical indications: Can justify studies in women of childbearing age and children in endemic areas with risk of exposure
- Needed studies for nonbiodefense clinical indications:
  - Studies in endemic anthrax areas

- Should include children (for example, young boys as herdsman)
- Ethical concerns: Could not be tested in countries with no perceived risk of exposure
- Recommended "next steps":
  - Epidemiological and feasibility information in endemic areas
  - Test in children where exposure endemic
  - No recommendations for testing in pregnancy
- Are there "compassionate use" contingencies in case of an emergency? Yes, with antibiotics.

The Vaccines Subgroup reported the following for currently deployed smallpox vaccines:
- Vaccine description: ACAM2000 cloned NYCBOH vaccinia virus passed in tissue culture
- Evidence for biodefense clinical need: Potential for weaponization
- Nonbiodefense clinical need(s): Only in laboratory where exposure to orthopoxviruses occurs
- Current FDA approved or EUA Indications: Yes to both
- Administration requirements/dosing: Licensed preparation using bifurcated needle, single dose
- Is postexposure administration projected to have benefit?
  - Yes, within 4 days complete protection
  - Within 6 days may modify progression
- Current FDA or EUA authorized age groups:
  - Approved for pregnant women? Yes if exposed or at immediate risk of exposure
  - Experience in children younger than 18 years? Yes
  - Dose response in different age groups? Yes, adverse events
- Current available formulations/shelf life: ACAM2000, very long if like Dryvax
- Adverse events (short-term) associated with vaccine administration:
  - Fever attributable to vaccine: Low grade, 5–10 percent
  - Local reactions (swelling, inflammation): Pain and local reactions
  - Other: Encephalitis, more severe in infants, ezcema vaccinatum, progressive vaccinia, myocarditis and pericarditis, infection of fetus possible if mom unprimed
- Adverse events (long-term) associated with the vaccine:
  - Any reasons to suspect the consequences would be different in children? Incidence of some post vaccinia complications higher in younger age groups
  - Any reasons to suspect the consequences would be different in pregnant women? Potentially for fetus
- Relevant current ongoing clinical trials: None with licensed product
- Ethical concerns: High frequency of serious reactions
- What are the conditions for emergency use in persons younger than 18 years and in pregnant women? Postexposure
- Recommended "next step": Press ahead with antiviral ST-246 now available for immunocompromised patients.

The Vaccines Subgroup reported the following for new smallpox vaccines undergoing studies:
- Biodefense therapeutic area: Smallpox
- Vaccine description:
  - MVA (IMVAMUNE)—attenuated vaccinia virus nonreplicating in human tissues—frozen

- NYVAC—attenuated vaccinia virus nonreplicating in human tissues further attenuated vaccinia with deletion of 18 genes, lyophilized
  - LC16M8—further attenuated from Lister strain in Japan with deletion of about 15 percent of genome, refrigerator temperature
- Evidence for biodefense clinical need:
  - Threat of bioattack, about 15 tons from former Soviet Union lost
  - Nonbiodefense clinical need(s): Lab personnel, areas with endemic monkeypox
- Administration requirements/dosing:
  - Varies with preparation
  - MVA, NYVAC require at least two IM doses
  - LC16M8 thought to be similar to Dryvax; single dose with bifurcated needle, but FDA is not sure, could be explored in animal
  - Is postexposure administration projected to have benefit? Yes
- Status of current clinical trials:
  - Does the dose response in different age groups vary (including children)? Do not believe dose response differs except for adverse events. Trials are in progress but not using Dryvax or ACAM2000, most dealing with use of MVA as vector for genes from other pathogens; may be beneficial (HIV, malaria, tuberculosis); vaccinia antibody and CMI measurements should be available from dose response studies in young adults
  - Is there any experience in pregnant women? No, but likely to be used postevent
  - Adverse events (short-term) associated with vaccine administration: Systemic and local reactions minimal for MVA and NYVAC; thought to be better tolerated than licensed product
- Adverse events (long-term) associated with the vaccine:
  - Any reasons to suspect the consequences would be different in children? No
  - Any reasons to suspect the consequences would be different in pregnant women? No
- Relevant ongoing clinical trials, designated new trials: Trials cited above (MVA and NYVAC) with complex vaccine
- Needed additional studies for children and pregnant women for biodefense clinical indications:
  - Additional studies needed to evaluate immune response in pregnant women and children where MVA or NYVAC is vector
  - Looking at accelerated immune responses for postexposure situations want good immune response within 28 days
  - MVA needs to remain cold, which requires a frozen chain
  - Evaluate use in immunosuppressed individuals (trials in HIV patients underway)
  - Evaluate in monkeypox prevalent areas
- Needed studies for nonbiodefense clinical indications: Studies in endemic monkeypox areas
- Ethical concerns: Testing in populations where no immediate risk of exposure
- Recommended "next steps":
  - Studies where monkeypox is prevalent
  - Collect data from vector studies
  - No recommendations for testing in pregnancy
- Are there "compassionate use" contingencies in case of an emergency? ACAM2000 following orthopoxvirus exposure.

Antibiotics/Antivirals/Antitoxins. The Antibiotics, Antivirals, and Antitoxins Subgroup reported the following. The U.S. public health system and primary health care providers must be prepared to address varied biological agents, including pathogens that are rarely seen in the United States. Highest priority agents (Category A) include organisms that pose a risk to national security because they can be easily disseminated or transmitted person-to-person; cause high mortality, with potential for major public health impact; might cause public panic and social disruption; and require special action for public health preparedness. Category A agents include:

- Variola major (smallpox)
- *Bacillus anthracis* (anthrax)
- *Yersinia pestis* (plague)
- *Clostridium botulinum* toxin (botulism)
- *Francisella tularensis* (tularemia)
- Filoviruses
  - Ebola hemorrhagic fever
  - Marburg hemorrhagic fever
- Arenaviruses
  - Lassa (Lassa fever)
  - Junin (Argentine hemorrhagic fever) and related viruses.

The Antibiotics/Antivirals Subgroup recommended the following medical therapy for children with clinically evident inhalational anthrax infection in the contained casualty setting (from Inglesby et al., 1999):

- Initial therapy: Ciprofloxacin, 20–30 mg/kg per day IV divided into two daily doses, not to exceed 1 g/day
- Optimal therapy if strain is proven susceptible
  - Age < 12 years: penicillin G, 50,000 U/kg IV every 6 hours
  - Age ≥ 12 years: penicillin G, 4 million U IV every 4 hours.

The Antibiotics/Antivirals Subgroup recommended the following medical therapy for children with clinically evident anthrax infection in the mass casualty setting or for prophylaxis (from Inglesby et al., 1999):

- Initial therapy: Ciprofloxacin, 20–30 mg/kg per day by mouth divided into two daily doses, not to exceed 1 g/day
- Optimal therapy if strain is proven susceptible
  - Weight ≥ 20 kg: amoxicillin, 500 mg by mouth every 8 hours
  - Weight < 20 kg: amoxicillin, 40 mg/kg divided into three doses to be taken every 8 hours.

The Antibiotics/Antivirals Subgroup recommended the following treatment of pneumonic plague in the contained setting for children (from Inglesby et al., 2000):

- Preferred choices
  - Streptomycin, 15 mg/kg IM twice daily (maximum daily dose, 2 g)
  - Gentamicin, 2.5 mg/kg IM or IV three times daily
- Alternate choices

- Doxycycline
    - If ≥ 45 kg, give adult dosage
    - If < 45 kg, 2.2 mg/kg IV twice daily (maximum, 200 mg/day)
- Ciprofloxacin, 15 mg/kg IV twice daily
- Chloramphenicol, 25 mg/kg IV four times daily.

The Antibiotics/Antivirals Subgroup recommended the following treatment of pneumonic plague in the mass casualty settings and postexposure prophylaxis for children (from Inglesby et al., 2000):
- Preferred choices
    - Doxycycline
        - If ≥ 45 kg, give adult dosage
        - If < 45 kg, 2.2 mg/kg orally twice daily
    - Ciprofloxacin, 20 mg/kg orally twice daily
- Alternate choice:
    - Chloramphenicol, 25 mg/kg orally four times daily.

The Antibiotics/Antivirals Subgroup recommended the following treatment of tularemia in the contained setting for children:
- Preferred choices
    - Streptomycin, 15 mg/kg IM twice daily (maximum daily dose, 2 g)
    - Gentamicin, 2.5 mg/kg IM or IV three times daily
- Alternate choices
    - Doxycycline
        - If ≥ 45 kg, 100 mg IV twice daily
        - If < 45 kg, 2.2 mg/kg IV twice daily
    - Ciprofloxacin, 15 mg/kg IV twice daily
    - Chloramphenicol, 15 mg/kg IV four times daily.

The Antibiotics/Antivirals Subgroup recommended the following treatment of tularemia in the mass casualty settings and postexposure prophylaxis for children:
- Preferred choices
    - Doxycycline
        - If ≥ 45 kg, 100 mg orally twice daily
        - If < 45 kg, 2.2 mg/kg orally twice daily
    - Ciprofloxacin, 15 mg/kg orally twice daily.

The use of tetracyclines in pediatric patients has been limited because these drugs can cause permanent dental discoloration in children younger than 8 years of age. The period of odontogenesis to completion of formation of enamel in permanent teeth appears to be the critical time for the effects of these drugs and virtually is complete by 8 years of age, at which time the drug can be given without concern for dental staining. The degree of staining appears to depend on dosage and duration of therapy, with the total dosage received being the most important factor. Tetracyclines also may cause enamel hypoplasia and reversible delay in rate of bone growth.

These possible adverse events have resulted in use of alternative, equally effective antimicrobial agents in most circumstances in young children in which tetracyclines are likely to be effective. However, in some cases, the benefits of therapy with a tetracycline can exceed the risks, particularly if alternative drugs are associated with significant adverse effects or may be less effective. In these cases, the use of tetracyclines in young children is justified. Examples include life-threatening rickettsial infections such as Rocky Mountain spotted fever, ehrlichiosis, cholera, and anthrax. Doxycycline usually is the agent of choice in children with these infections; chloramphenicol or a fluoroquinolone are alternatives.

The Antibiotics/Antivirals Subgroup reported the following for children:
- Biodefense therapeutic area: Antibacterials
- Biodefense therapeutic agent/device:
  - Doxycycline and ciprofloxacin for plague, anthrax, and tularemia
  - Gentamicin for plague and tularemia
- Biodefense clinical need:
  - Doxycycline PK in children younger than 8 years old
  - Ciprofloxacin PK for children younger than 1 year old
  - Gentamicin once-a-day dosing
- Nonbiodefense clinical need(s): Treatment of Rocky Mountain spotted fever, *Brucella*, *Bartonella*, cholera, etc., in children; sepsis.

The Antibiotics/Antivirals Subgroup reported the following for doxycycline and ciprofloxacin:
- Biodefense therapeutic area: Antibacterials
- Biodefense therapeutic agent/device:
  - Doxycycline, IV and orally, FDA-approved for all three biological agents
  - Ciprofloxacin, IV orally, FDA-approved for anthrax, EUA for plague/tularemia
- Biodefense clinical need: Postexposure prophylaxis
- Current FDA-approved indications and dosing:
  - Doxycycline: Rickettsial diseases, sexually transmitted infections/pelvic inflammatory disease, various bacterial respiratory diseases, some ophthalmic infections
  - Ciprofloxacin: Adult urinary tract infections, appropriate lower respiratory tract infections, intra-abdominal infections, infectious diarrhea, bone and joint infections
- Current FDA-authorized age groups:
  - Doxycycline: Adults and children older than 8 years
  - Ciprofloxacin: Adults and children 1–17 years
- Mechanism of action, available age-related PK data:
  - Doxycycline
    - Absorption: Nearly 100 percent absorbed orally
    - Distribution: Widely distributed, medium to high polypeptide (PP) binding
    - Clearance: $T_{1/2}$ 18–22 hours
    - Renal: 40 percent cleared by kidney
    - Hepatic: concentrations in liver and bile
  - Ciprofloxacin
    - Absorption: 70 percent BA with oral absorption, minimal first-pass effect

- Distribution: 20–40 percent PP binding, wide distribution, concentrations in the urogenital system
- Clearance: $T_{1/2}$ 4 hours
- Renal: Predominant mechanism (40–50 percent unchanged in urine), active renal tubular excretion
- Hepatic: inhibitor of cytochrome P450 (CYP1A2)
- Needed studies for biodefense clinical indication:
  - Doxycycline: PK data for appropriate dosing
  - Ciprofloxacin: PK data for appropriate dosing
- Needed studies for nonbiodefense clinical indications:
  - Rare indications for doxycycline—occasional rickettsial infection in pregnancy
  - Quinolones for upper urinary tract infections in pregnancy
  - Quinolones for gonococcus in pregnancy and β-lactam (cephalosporin allergy)
    - Rare, single-dose, resistance
- Relevant ongoing clinical trials:
  - None known for pregnant population
  - Obstetric Pharmacology Research Unit Network opportunistic study
- Other considerations:
  - Amoxicillin: May be inadequate for postexposure prophylaxis
  - Ceftriaxone
    - Alternative treatment for plague
    - Used for pyelonephritis treatment in pregnancy
  - Azithromycin
    - Hypothetical treatment agent for *Burkholderia mallei*
    - Used for chlamydia in pregnancy
  - Clindamycin
    - Hypothetical treatment for anthrax
    - Used for intrauterine infection in pregnancy in penicillin-allergic patients
  - Oseltamivir: Studies in progress, treatment and PK
  - Down the road
    - ST-246 for smallpox
    - Cidofovir for smallpox
    - Cethromycin as a broad-spectrum agent for anthrax, plague, and tularemia
      - Low potential for resistance development
- Ethical concerns and study challenges:
  - Doxycycline: Category D, compatible with breast-feeding
  - Ciprofloxacin: Category C, likely compatible with breast-feeding
  - Pregnancy studies in general; difficult if no disease
    - Risk-benefit ratio challenging without clinical disease
    - Heightened concern without great understanding of situation
      - IRBs, media, lay persons
      - Chest x-rays in pregnancy, antidepressants, etc.
  - Time-held dictums with or without great data:
    - Doxycycline (teeth staining); quinolones (cartilage impairment)
  - Fighting biosecurity fatigue of funders, IRBs, society

- No outbreak is good…"nonjustifiable expenditures."

The Antibiotics/Antivirals Subgroup reported the following for antibacterials in pregnancy:
- Biodefense therapeutic area: Antibacterials in pregnancy
- Biodefense therapeutic agent/device: Doxycycline, ciprofloxacin, and gentamicin once-a-day dosing
- Biodefense clinical need: Anthrax, tularemia, and plague
- Nonbiodefense clinical need(s): Sepsis
- Other issues:
  - Personal preparedness kit: antibiotics for children and pregnant women should be studied
  - Antivirals: mechanisms at FDA for pediatric studies in place
- Therapeutic agents:
  - Amoxicillin
  - Ciprofloxacin
  - Doxycycline
- Dosing recommendations:
  - Amoxicillin for children for anthrax
  - Palatability of suspensions for children
  - Additions to the stockpile, such as chloramphenicol
- Study recommendations:
  - Doxycycline: Pregnancy and children younger than 8 years for anthrax
  - Ciprofloxacin: Children younger than 1 year and pregnancy
- Potential additional bacterial threat agents for discussion:
  - *Yersinia pestis*
  - *Francisella tularensis*
  - *Burkholderia mallei, Burkholderia pseudomallei*
  - *Rickettsia*
- Antiviral development:
  - Oral prodrug of cidofovir for smallpox therapy (currently in phase 1 adult trials)
  - Looking to treat adenovirus in children with stem cell transplants
  - ST-246 for smallpox
  - T705—broad-spectrum antiviral active against flu and H5N1 and *in vitro* against bunyaviruses
  - Tamiflu testing in younger infants.

Radiation Working Group Report

The overall objectives of the Radiation Working Group were to:
- Make recommendations for administration criteria and dosing for children
  - Benchmark adult recommendations on the Radiation Event Medical Management (REMM) Web site (www.remm.nlm.gov)
- Make recommendations for the SNS
  - Pediatric formulations
- Identify areas for research and development.

The Radiation Working Group recommended the use of REMM management and exposure algorithms for the diagnosis and management of ARS. The current radiation management algorithm is comprehensive for adults. The REMM and Radiation Injury Treatment Network (RITN) algorithms provide an excellent foundation for a pediatric approach to acute radiation injury. Details are needed for pediatric and maternal/fetal scenarios. Areas of focus are:
- Dosimetry: Validate biomarkers in pediatric population
- Growth factors: Clarify pediatric labels or planned use
- Antibiotics: Clarify prophylaxis and febrile neutropenia recommendations
- Stem cell transplantation: Make appropriate recommendations from National Marrow Donor Program (NMRP) and American Society for Blood and Marrow Transplantation (ASBMT).

High priorities for pediatric dosimetry biomarker development are as follows:
- Candidate genotoxicity biomarkers
  - Gamma H2AX
  - Micronuclei assays
  - Gene expression and proteomic arrays
  - Metabolomic markers
  - Electron paramagnetic resonance spectroscopy
  - Glycophorin A, RAS, comet
- Host polymorphisms: modifying factors
  - Oxidant metabolism, DNA repair, inflammation
- Target research population and objectives
  - Pediatric age groups receiving x-ray therapy as part of stem cell transplantation conditioning regimens
  - Correlation with toxicity and polymorphisms
  - Correlation with parallel adult data.

High priority areas for pediatric research of hematopoietic syndrome/growth factors are:
- First priority clinical studies: FDA-licensed hematologic and mucosal protectant drugs
  - Filgrastim (Neupogen)
  - PEG-filgrastim (Neulasta)
  - Romiplostim (Nplate)
  - KGF (Palifermin)
  - Combination studies
- Future clinical studies: late phase in adults
  - PEG-thrombopoietin
  - Human growth hormone.

Key elements of recommendations for antibiotics are:
- Febrile neutropenia
  - Infectious Diseases Society of America recommendations
  - Expanded investigation of oral antibiotics for continuation therapy of low-risk febrile neutropenia
- Prophylaxis: Final revisions in process, including pediatric and pregnancy recommendations.

Recommended prophylactic agents are:
- Fluoroquinolone: Pediatric research recommendation
- Fluconazole
- Acyclovir (if positive herpes simplex virus history or seropositive)
- Intervention: Absolute neutrophil count < 500 or significant exposure.

With regard to stem cell transplantation, the Radiation Working Group recommends following the RITN-NMDP/ASBT guidelines.

With regard to countermeasure agents for internal decontamination, the Radiation Working Group recommends review of SNS for:
- Pediatric formulations
- Assessment of adequacy of pediatric/maternal-fetal pharmacology and toxicity
- Gap analysis of portfolio for children
- Identification of target areas for research.

Agents for review include D-penicillamine, potassium iodide, Prussian blue, bicarbonate, and calcium/zinc DTPA.

New agents recommended for pediatric radiation research initiatives include:
- FDA approved for other indications or late phase adult studies
- Pulmonary syndrome and fibrosis
  - KGF (Palifermin)
  - Pentoxyfylline
  - Pirfenidone plus vitamin E
  - Imatinib
  - Statins
- Gastrointestinal syndrome
  - KGF (Palifermin)
  - Statins
  - Mesenchymal stem cells.

In determining which agents are worthwhile to study in children, key issues for consideration from adult studies are as follows:
- Efficacy and timing/duration of therapy required for effect
- Toxicity
- Degree of efficacy—number needed to treat for benefit
- Who will benefit (for example, exposure, age)
- Logistics.

Recommendations for research coordination and early drug development include:
- Research in radiation injury in juvenile preclinical model systems
  - Comparison with adult preclinical models
  - Development and piloting exposure biomarkers
- Evaluation of new agents in preclinical development and early phase adult clinical trials

- – Juvenile preclinical models
- – Mechanism for dedicated rapid critical review of adult studies for rapid development to pediatric population
- Formation of pediatric bioterrorism/radiation advisory committee
  - – Expert panel to advise NIH and DoD on continuing basis
    - – Responsible for radiation countermeasure drug development plans for children and pregnant women
  - – Focused on pediatric and maternal/fetal unique issues in basic and translational research, implementation/deployment
  - – Pediatric drug formulations and SNS
  - – Coordinate research between related federal initiatives and agencies.

Action items, assignments, and timeline include:
- Growth factors/hematopoietic syndrome: Drug recommendations
- Infection
  - – Treatment recommendations
  - – Prophylaxis recommendations
- Special considerations and care modifications
  - – Pregnant women/fetuses
  - – Trauma
- New drugs/topic areas for investigation
  - – Drugs/therapeutics
    - – New
    - – PK of existing drugs
- Dosimetry/biomarkers
  - – Exposure measure pediatric validation
  - – Diagnostics.

The Radiation Working Group recommends the investigation of the following classes of new drugs that are approved by FDA for other indications:
- ACE inhibitors
- Angiotensin II receptor antagonists.

The Radiation Working Group listed the following potential drugs for investigation that are approved by FDA. Other indications include:
- Statins and radiation protection
- Pentoxyfylline and alpha-tocopherol (vitamin E)
- Pirfenidone.

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