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NIH's Response to the Global Outbreak of Severe Acute Respiratory Syndrome (SARS)

Statement of

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Mr. Chairman and Members of the Committee, thank you for the opportunity to discuss how the National Institutes of Health (NIH) is responding to the global outbreak of Severe Acute Respiratory Syndrome, or SARS. I am pleased to appear today with my colleagues from our sister agencies, within the Department of Health and Human Services. As of May 14, 2003, 7,628 cases of SARS have been reported across the globe, with 64 probable cases identified in the United States; there have been no deaths from SARS thus far reported in the United States. The relatively low number of probable cases reported in the United States is likely the result of early diagnoses and effective public health measures put in place by the CDC and state and local health authorities to contain the imported SARS cases and prevent secondary transmissions.

While travel alerts and advisories and recommended infection control measures can help slow the progression of the SARS epidemic, these alone are not long-term solutions to this new and unpredictable disease. Instead, we must develop safe and effective treatments and vaccines that can protect the American people. The SARS epidemic is still evolving and it is unclear whether the incidence of the diseases will decline, plateau or accelerate. Therefore we must be prepared for any eventuality.

Like HIV/AIDS, Ebola and West Nile virus, SARS reminds us that emerging and reemerging infectious diseases are constant threats to national and international public health. Dr. Gerberding and her CDC team, together with the World Health Organization (WHO) and others, have done an outstanding job in identifying and tracking the SARS epidemic, illuminating the clinical features and etiology of the disease, and providing the world with information about the epidemic in real time.

Complementing the efforts of the CDC and WHO, the National Institute of Allergy and

Infectious Diseases (NIAID), a component of NIH, has a significant role in the efforts against SARS, notably in diagnostics, therapeutics and vaccine development, drug screening, and clinical research. As has been the case with other emerging infectious diseases, we anticipate that the strong NIAID research base in disciplines such as microbiology, immunology and infectious diseases will facilitate the development of new interventions to help counter SARS.

The CDC and WHO have accumulated evidence, which we now believe is close to definitive, that SARS is caused by a novel coronavirus that may have crossed species from an animal to humans, although this latter point has certainly not been proven. This hypothesis is based on the detection and isolation of coronaviruses from unrelated SARS patients from different countries and on the finding that SARS patients mount an immunological response to coronavirus as they proceed from the acute illness to the recovery or convalescent stage. Furthermore, data from the Netherlands show that non-human primates infected with this coronavirus develop a SARS-like disease, suggesting that this virus is the cause of SARS. Although some questions remain, the strong evidence for a causative role for a coronavirus has prompted the ongoing development of diagnostic tools, therapies, and vaccines that target coronaviruses.

Coronaviruses are best known as one of the causes of the common cold, a benign condition that very rarely results in life-threatening disease. The coronavirus associated with SARS is a type of coronavirus, possibly of animal origin, that has not been previously identified.

NIAID Research on SARS

NIAID maintains a longstanding commitment to conducting and supporting research on

emerging infectious diseases, such as SARS, with the goal of improving global health. In carrying out its global health research mission, the Institute supports a myriad of activities, including intramural and extramural research and collaborations with international agencies and organizations.

Since the earliest indications that we were dealing with a new disease, very likely caused by a newly recognized virus, the NIAID has marshaled its resources to rapidly initiate the development of diagnostics, therapeutics, and vaccines against SARS. NIAID has assembled a multi-disciplinary working group to develop a broad-based program that addresses the research needed to combat SARS. Key intramural laboratories have begun to pursue a range of research strategies to develop a SARS vaccine as well as therapeutics, including immune-based therapies, and our extramural programs are poised to help as well. We also have initiated and expanded collaborations with our colleagues in other federal agencies, academia, and private industry. In addition, NIAID recently released three "Sources Sought" announcements, a special mechanism to rapidly identify contractors who can develop treatment strategies, vaccines, and antibody preparations to address SARS.

On May 30, 2003, NIAID will host a scientific workshop at the NIH campus in Bethesda, Maryland, to address SARS research needs. The workshop will feature international experts in the fields of coronavirus biology, vaccine development, antiviral drug development, laboratory diagnosis, SARS epidemiology, etiology, and clinical management. The purpose of this meeting is to identify the scientific, technical, and other challenges that must be addressed to develop vaccines, antiviral therapeutics, and other interventions in response to SARS.

Surveillance and Epidemiology

NIAID supports a long-standing program for the surveillance of influenza viruses in Hong Kong, led by Dr. Robert Webster of St. Jude's Children's Research Hospital in Memphis. Dr. Webster and his team in Hong Kong have collaborated with WHO, CDC, and others in helping to illuminate the SARS outbreaks in Asia. At the request of WHO, NIAID assigned a staff epidemiologist to provide technical assistance during the early stages of the epidemic. In addition to global surveillance activities, NIAID will support epidemiological studies of populations at potentially greater risk for SARS, including individuals with HIV/AIDS.

Diagnostics Research

As Dr. Gerberding has indicated, the CDC already has made significant progress in developing diagnostic tests for SARS. As part of these efforts, NIAID-sponsored researchers in Hong Kong also devised a diagnostic test based on polymerase chain reaction (PCR) technology as well as a diagnostic tool using the immunofluorescence assay technique. In other research, the NIAID-funded Respiratory Pathogens Research Unit (RPRU) at Baylor College of Medicine has developed methods to detect known human coronaviruses using cell culture and molecular diagnostic tools and can also assess the host immune response to known coronavirus infections. During this calendar year, NIAID will expand this capacity for research on emerging acute viral respiratory diseases. Also, NIAID is using existing funding mechanisms, such as the contract with St. Jude's Hospital, to help support the development of other sophisticated diagnostic tools.

It is anticipated that a sensitive and specific diagnostic test for SARS may be available within six to 12 months. Within one to three years, it may be possible to develop a

rapid, accessible easy-to-use test for SARS that could be widely deployed in diverse healthcare settings.

Vaccine Research

As the SARS epidemic continues, it will be necessary to consider a broad spectrum of vaccine approaches. NIAID is supporting the rapid development of vaccines to prevent SARS through both our extramural and intramural programs, including the NIAID Vaccine Research Center on the NIH campus. NIAID scientists have received samples of the SARS coronavirus from CDC and have already successfully grown the virus in cell culture, a first step towards developing a vaccine. Initial efforts have focused on the development of an inactivated (or killed) virus vaccine. As more knowledge about SARS becomes available, other types of vaccine candidates will soon follow, including novel approaches such as vector-based and recombinant vaccines, DNA-based vaccines, and live-attenuated vaccines.

Fortuitously, vaccines against common veterinary coronaviruses are routinely used to prevent serious diseases in young animals, such as a vaccine given to pigs to prevent serious enteric coronavirus disease. Insight from veterinary coronavirus vaccines could prove useful as we develop vaccines to protect humans.

To accelerate SARS vaccine research and development efforts, NIAID has initiated contracts and other relationships with companies, institutions and other organizations with specialized technologies, cell lines and containment facilities relevant to SARS research for the purpose of supporting the development of reagents needed for vaccine development, and developing animal models such as mice and relevant species of monkeys. For example, the NIAID Vaccine Research Center recently expanded an

existing agreement with GenVec, a biopharmaceutical company in Gaithersburg, Maryland, to begin the development of a candidate vaccine against SARS. NIAID is negotiating with other companies to develop additional candidate vaccines. Another important component of SARS vaccine research will be to identify ways to generate mucosal immunity against the SARS coronavirus.

Within the next six to 12 months, NIAID anticipates that it will be possible to demonstrate whether an inactivated vaccine against SARS is a workable concept, e.g., to show that we can protect a monkey against the SARS virus. If so, Phase I trials of such a candidate vaccine can be accelerated. If research and development proceed on schedule and if animal testing is successful, a first-generation inactivated SARS vaccine could become available within several years.

Therapeutics Research

With the emergence of SARS, NIAID responded rapidly to a request from CDC to evaluate candidate antiviral agents through a collaborative antiviral drug-screening project at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID). To date, NIAID has supplied approximately 40 FDA-approved antiviral drugs to USAMRIID such that their efficacy against the SARS coronavirus can be evaluated. The Institute also is pursuing the development of novel antivirals, such as compounds that block viral fusion with and entry into host cells. In addition, NIAID has initiated discussions with the pharmaceutical industry about candidate antiviral drugs already in the research "pipeline," and is reviewing a proposal for a clinical trial of antiviral therapy to be conducted by investigators of the NIAID Collaborative Antiviral Study Group and the NIH Clinical Center.

In addition to antiviral drugs, NIAID is supporting the development of passive immunotherapy (monoclonal and polyclonal antibodies) as a therapy for SARS. Within the next one to three years, it may be possible to have available therapeutic monoclonal antibodies for SARS.

Clinical Research

Clinicians treating SARS patients have not yet identified treatment strategies that consistently improve prognosis, beyond good supportive and intensive care. Conventional antibiotics do not work, a fact that is consistent with SARS being a viral disease. NIAID is pursuing several strategies to determine whether any existing drugs or combinations of treatments can simultaneously block viral replication and boost the immune response to the virus.

At the NIH Clinical Center in Bethesda, MD, and through the NIAID Collaborative Antiviral Study Group, NIH is developing protocols to admit SARS patients for evaluation and treatment, should this become necessary. This will be an opportunity to evaluate the pathogenesis of the illness and the efficacy of antiviral and immune-based therapies in patients with SARS. We also plan to evaluate approaches to improve management of patients with severe forms of the disease, such as the passive transfer of antibodies from SARS patients who have recovered from the disease.

In addition to ensuring state-of-the-art treatment of potential patients, our clinical experts will be able to study the clinical characteristics of patients with SARS. We are particularly interested in answering key questions about the disease mechanisms of SARS. For example, are severe outcomes such as acute respiratory distress and mortality entirely caused by the presence of virus, or does the immune system play a

role in causing the severe outcomes in some patients? What are the sites and the duration of viral shedding? What is the nature of the immune response? These are central questions to address because they may open up avenues for treatment as well as better preventive strategies.

Basic Research

NIAID's long-standing commitment to and investment in emerging disease research is allowing us to expeditiously pursue research on SARS. For example, NIAID continues to support the Emerging Viral Disease Research Centers, which have been conducting SARS antibody studies and will be able to assist in the development of animal models for SARS. NIAID currently is supporting 18 grants on coronavirus research. Also, the study of patients, as well as specimens in NIAID laboratories, will facilitate our understanding of the natural history of the SARS virus and its potential animal reservoir, and help illuminate the risk factors and epidemiology of SARS. NIAID will support and conduct basic research studies on the pathogenesis of the disease and viral replication mechanisms, in order to identify targets for antiviral drugs, diagnostic tests, and vaccines. Finally, the Institute will support and conduct genomic sequencing, proteomics, and bioinformatics of coronaviruses.

The identification or development of animal models that mimic human SARS is critical to our understanding of the SARS virus and how it causes disease. Of note, an existing NIAID animal model of a virus infection that causes a disease in mice very similar to SARS has been identified. The relevance of this animal model to SARS will be evaluated and may prove an important tool for defining treatment approaches that involve modulation of the immune system. NIAID will also support the development of other relevant animal models for SARS.

Infrastructure

A central concern when working with the SARS virus or SARS patients is the availability of facilities with the required safety level for the clinicians and staff, as well as for the community. Our ongoing plans to develop high-level containment facilities, towards which funds were appropriated in FY 2003, will facilitate SARS research, as well as planned studies of potential bioterror agents and other emerging diseases. Research with the SARS coronavirus will occur in Biosafety Level-3 facilities.

Conclusion

Mr. Chairman, thank you again for allowing me to discuss NIH's efforts to address SARS. Despite ongoing research and early successes, we still have much to learn about the disease. As you have heard, NIAID-sponsored coronavirus research, studies of other viral diseases, and clinical research already have positioned us well in our quest for tools to detect, treat, and prevent SARS. In the weeks and months ahead, NIH will continue to collaborate with our sister agencies, the CDC and the Food and Drug Administration, as well as other relevant agencies, to accelerate and expand our research aimed at improving the diagnosis, prevention, and treatment of SARS.

I would be pleased to answer your questions.