CONFERENCE SUMMARY

JAMES M. HUGHES, MD*

OVERARCHING THEMES OF THE CONFERENCE

The themes of the conference on emerging infectious diseases can be divided into five C's and 3 P's. The first C is for *complacency*. Many participants acknowledged that complacency regarding infectious diseases exists, but the conference presenters offered a good deal of what might be described as "gloom and doom" related to the challenge posed by microbial agents. I think it is fair to say that if any of the conferees were complacent about infectious diseases when they came to the conference, they were not complacent when they left.

The second C represents *challenges*. Dr. Lederberg pointed out that the central issue was "our wits versus their genes," and that it was not clear who was going to come out on top. Clearly, there is a need for innovative approaches to the detection of, and response to, infectious diseases. We need to look for opportunities, such as some in the managed-care arena, to place us in a position from which we will be able to address some of these issues more effectively.

The third C relates to the *critical* role of the laboratory. The modern microbiology laboratory was central to many of the presentations offered in the conference. The laboratory plays a critical role in surveillance, clinical diagnosis, and molecular epidemiology.

The fourth C refers to the recurrent theme of *capacity*. Many presenters noted that capacity is limited at the local level, the state level, the national level, and the international level as well. There are issues concerning lack of human resources, shortages of equipment, and shortages of diagnostic reagents. Problems with laboratory facilities, which we certainly face at the Centers for Disease

*Dr. Hughes is Director, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Mail Stop C-12, Atlanta, GA 30333.

Control and Prevention (CDC), are also encountered by many state health department laboratories. Insufficient capacity is associated with a critical need for training in epidemiology, microbiology, entomology, and research related to infectious diseases. It is no secret that people in charge of medical training are under pressure increasingly in this country. It is difficult to add infectious diseases, particularly anything that might be viewed as exotic, to the medical school curriculum. There are pressures now to train more generalists, rather than experts, in infectious diseases.

The fifth C is for *communications*. There are needs to communicate data, to communicate guidelines, and to be able to communicate with colleagues in other countries through the information superhighway and the use of tools such as ProMED. These needs are urgent and are largely unmet.

The first P refers to the critical need for *professional, public, and policymaker* education, a theme that was enunciated loudly and clearly. It is not enough, however, to focus solely on health care professionals. We must reach the public, and, clearly, there is an urgent need to reach and educate policymakers. A number of presenters pointed out that we must be proactive in this regard.

The second P is for *partnerships*. The need for coordination exists at the local, state, federal, and international levels. There is a need for clinicians and public health specialists to communicate with each other and for both groups to be able to communicate with academic researchers and workers in the pharmaceutical industry.

The final P is for the need to set *priorities*. Clearly, we cannot be all things to all people, as a number of presenters pointed out.

In the course of the conference, we did not hear much about another C, the *costs* of not addressing these issues. There were some exceptions. Conferees learned about what must be done to address the tuberculosis (TB) resurgence and the emergence of multiple-drug-resistant TB. We learned that nosocomial infections in this country are estimated to cost approximately \$4 billion annually. Ms. Garrett pointed out that the cost of the bubonic plague epidemic in India was estimated to be on the order of \$2 billion.

Another "cost" alluded to was terrorism involving biological agents. I think everyone needs to realize that a biologic incident would not present the way the chemical incident involving sarin presented in Tokyo. It was very easy to recognize that a chemical exposure had occurred and relatively easy to suspect that it was a result of terrorist action. If a biologic event occurs, it is likely to present as an unexplained severe illness, the source of which will be unclear because of

the incubation period involved and the fact that affected people likely will be dispersed before they become known. Nevertheless, the threat is real and deserves our attention.

GENERAL COMMENTARY

The World Health Organization estimates that approximately one-third of the deaths in the world in 1993 were caused by infections and parasitic diseases. Because some infections are grouped in other categories of disease, that figure underestimates the true burden of infectious disease mortality locally. Specific infectious causes of death were acute respiratory infection, 4.1 million; tuberculosis, 2.7 million; malaria, 2 million; measles, 1.2 million. These diseases do not generate the kind of intense interest and concern that plague or Ebola do, but they are major global public health problems.

In their presentations at the conference, Dr. Lederberg and Dr. Hamburg reminded us that we live in a global village, and that any attempt to distinguish domestic infectious disease issues from international ones is artificial. Dr. Lederberg pointed out that he would regard the term *exotic diseases* as being outmoded.

We should not forget that infectious diseases are an important contributor to mortality in the US as well. Dr. Hamburg pointed out that HIV infection and AIDS have become a leading cause of death in this country for persons between the ages of 25 and 44.

Among the many excellent Institute of Medicine reports, I have a personal favorite: *Emerging Infections: Microbial Threats to Health in the United States*.¹ I commend Dr. Lederberg and Dr. Shope and all their colleagues who developed this excellent report, not only for the work itself, but also for their incredible sense of timing: the report was published two months before the *Escherichia coli* O157:H7 Jack-in-the-Box foodborne outbreak occurred in four western states. We, and colleagues throughout the country, have not had time to take a deep breath since.

The six factors that the committee identified that contribute to infectious disease emergence and re-emergence have stood the test of time. It is microbial adaptation and change that make infectious diseases unique. In terms of human demographics, Ms. Garrett's identification of the megacities, the huge, sprawling urban areas, particularly those located in the developing world, give one pause when reading about them and even more so when visiting them: one can see easily the circumstances that facilitate the transmission of infectious agents. In a related concept, Dr. Ewald identified institutions as places from which new problems may emerge or re-emerge. He was thinking of hospitals. I also want

to include child day-care centers, a setting that did not receive a great deal of attention in this conference, but one that is a hotbed of respiratory and gastrointestinal infections. Increasingly, we are seeing them as settings in which drug-resistant organisms, particularly drug-resistant pneumococci, commonly are encountered.

Dr. McNamara addressed the question, How safe is our food? Dr. Soave talked about troubled water in New York City and, potentially, in other places, noting the outbreak of cryptosporidiosis in Milwaukee in the spring of 1993, an event that was recognized as the pharmacies were literally running out of antidiarrheal medication. Both Dr. McNamara and Dr. Soave pointed out that the national surveillance data on foodborne outbreaks and waterborne outbreaks are derived from the extremely insensitive passive surveillance systems; in surveillance systems for both, more than half of the outbreaks that are identified are of unknown etiology, suggesting that in many cases adequate laboratory capacity was not brought to bear on the investigations.

The hantavirus pulmonary syndrome epidemic that occurred in the Southwest in May 1993 was addressed by a number of speakers. The roles of the astute clinician and the astute pathologist, working in a medical-examiner setting to recognize the problem, were pointed out. This point should not be lost by any of us, nor should another, which was addressed in some of the questions raised in Dr. Shope's presentation: how did we identify the etiologic agent so rapidly once we got specimens at CDC?

It was not because we thought that we were going to find a hantavirus at the start of this investigation, I can assure you. Nevertheless, we recognized that a serious, unexplained illness was present, and we thought we needed to bring the capacity of the National Center for Infectious Diseases laboratories to bear on the problem as rapidly as possible, while simultaneously characterizing the illness and conducting epidemiologic investigations in the field. We felt that we should look for any evidence of any viruses that needed to be worked on under maximum containment. We were determined to pursue the problem, and we also were lucky. Two of our investigators, Dr. Ksiazek and Dr. Peters, were using reagents that had been developed as a result of years of US Army research focusing on hantavirus diseases in other parts of the world. We also were lucky in that these reagents cross-reacted with the virus causing this syndrome. Very early in the investigation, therefore, we had antibody evidence and, within a couple of days, data from polymerase chain reaction and sequencing, performed by Dr. Nichol, that strongly suggested that we were dealing with a previously unrecognized hantavirus. We consulted with hantavirus experts to confirm our

suspicion. Soon thereafter, we had immunohistochemical evidence from studies on autopsy tissue performed by Dr. Zaki. Six months later, we and colleagues at the US Army Research Institute for Infectious Diseases grew the virus in cell culture. This entire process points out the need to have adequate, sophisticated laboratory capacity and reagents available to address these issues.

Several presenters discussed drug resistance. Dr. Roberts and his colleagues presented important data, and Dr. Rahal pointed out the concerns about whether we might be entering the postantibiotic era. In the late 1970s when I was in training concerning infectious diseases, we literally could not keep up with all the antibiotics that were constantly appearing on the market. Today, fellows in infectious disease do not have that problem. In 1994, 22 new drugs were approved by the Food and Drug Administration for use in the US; of these, there were no agents for treatment of bacterial infections and no agents for treating fungal infections. Only two agents were approved for the treatment of certain viral diseases, each agent with very specific indications. The drug development pipeline has dried up: few agents and no new classes of antibiotics are close to becoming available. This fact makes doubly serious the problems now being seen with the increases in drug resistance in hospitals and in communities.

Much has been said about penicillin resistance in *Streptococcus pneumoniae*. It is instructive to note that, just as was the case for surveillance of drug resistance in *Mycobacterium tuberculosis*, CDC abandoned surveillance of drug resistance of *S. pneumoniae* in the mid-1980s. We are paying a large price for both decisions. We developed some limited data in 1987 that showed that the frequency of high-level penicillin resistance in *S. pneumoniae* was 0.02%. We took another look in 1991; by then, it had increased by a factor of more than 60, to 1.3%. Two years later, penicillin resistance had risen to 3.2%. At this conference on emerging infectious diseases, we learned about the New Jersey experience with this organism: it echoes the CDC experience a year before, in the Atlanta area, where, working with Dr. Toomey and her colleagues in the state health department, we observed that the frequency of high-level penicillin resistance in *S. pneumoniae* in the Atlanta metropolitan area was up to 7%. That information came as a surprise to clinicians working in Atlanta; I use it to highlight the need for clinicians to be aware of drug susceptibility patterns in their own geographic areas.

The problems associated with the lack of accurate surveillance data for community-acquired organisms and their susceptibility to antibiotics were clear from the presentations. They lead one to ask, "Why is infectious disease surveillance is so poor?" Of course, we must realize that we get what we pay for. Federal,

state, and local support provided for infectious disease surveillance in the US in 1992 included a total of \$74.6 million, of which \$42 million were contributed by the federal government. Most of those funds were used in four categorical disease areas: HIV, tuberculosis, sexually transmitted diseases, and some vaccine-preventable diseases, leaving less than 5% of the remaining federal dollars for surveillance of all other infectious diseases. State and local health departments were able to make up for some of this shortfall, but even so, only about 15% of the \$74.6 million spent on infectious disease surveillance was spent on infectious diseases not included in the four categorical disease areas. It is no surprise, therefore, that the data are as limited as they are. In 12 states in 1992, no time was spent on surveillance of foodborne or waterborne disease.

The resurgence of bubonic plague was noted during the conference. One thought might be offered to those who think that "it can't happen here": there are eight quarantine stations in the US; one of them happens to be at John F. Kennedy Airport, one of the gateways to New York City. That station is staffed by approximately six people. When one considers the volume of international travelers that come through Kennedy Airport, it should be clear that we do not have very good surveillance of returning travelers at ports of entry.

Dr. Bremen shared some very valuable data from his experience with Ebola in Zaire in 1976, and Dr. Lederberg commented on the ongoing situation there now. The global capacity to address this issue is limited. Dr. Lederberg mentioned that they were having difficulty finding the second wave of people to send to assist in the investigation. There are not very many people in the world who are experienced in dealing with this agent in the laboratory or in the field.

At the time of this outbreak, there were six maximum-containment laboratories in the world: two in the US, one in England, one in South Africa, and two in Russia. These are the institutions that have the facilities, supplies, and protective equipment that are needed to work with highly lethal agents. If the hantavirus episode in New Mexico had occurred in the spring of 1995 rather than in the spring of 1993, I can assure you that CDC would not have been able to handle both crises simultaneously.

Some lessons from our experience with plague apply equally well to Ebola. They stress the importance of surveillance for diseases in distant places. It was impossible to predict that plague would appear in Beed district and in Surat, India, in 1994, just as it was impossible to predict that Ebola would appear in Kikwit in 1995. The need for prompt epidemiologic investigation and adequate laboratory capacity could not be clearer. The global implications of a local problem

in a faraway place also should be very clear to us all. Finally, the disruption of commerce and industry that occurred in India as a result of the plague outbreak was dramatic.

THE RESPONSE OF THE CENTERS FOR DISEASE CONTROL AND PREVENTION

An emerging infections plan has been developed by CDC; it was published in the spring of 1994.² Dr. Hamburg and Ms. Garrett both mentioned the four goals in the plan. They focus on (1) surveillance and response, (2) applied research, (3) prevention and control, and (4) infrastructure needs at the local, state, federal, and international levels.

Sometimes, people think that CDC focuses exclusively on surveillance. That is not true, but we do believe that the plan must start with strengthening surveillance. However, there also needs to be a response capacity, and other issues need to be addressed as well.

We have estimated that full implementation of the CDC emerging infections plan would cost \$125 million a year. We believe that the plan can be implemented incrementally; we have obtained some resources that have enabled us to begin implementation.

Four Emerging Infection Programs were established by CDC in fiscal year 1995; one of them is in Connecticut under the leadership of Dr. Cartter and his colleagues. They initially had two core projects in common and additional projects of local priority. One of the core projects focuses on unexplained deaths in healthy children and young adults between the ages of 1 and 49; the second addresses invasive bacterial diseases. In 1996–1997, three additional Emerging Infections Programs (Georgia, Maryland, and New York) and a third core project, addressing foodborne diseases, were added.

Under the able editorship of Dr. Joseph McDade, CDC has begun publication of a journal, *Emerging Infectious Diseases*. Through a peer-review process that involves an editorial board of experts, the journal provides timely information on the theme of emerging infectious diseases. The journal is published quarterly and is available over the Internet (<http://www.cdc.gov/ncidod/EID/index.htm>) through the CDC home page (<http://www.cdc.gov>) and by hard copy.

The importance of partnerships in developing its plan was emphasized by CDC. Discussions were held—and partnerships are evolving—with local, state, and territorial health departments, with other federal agencies, with other countries and international organizations, and with public and private organizations, industry, academic institutions, and the clinical community. These associations

are forming because of the nature of the challenges that we all share; clearly, we must learn how to work together to address them effectively.

The Committee on International Science, Engineering, and Technology is one of nine committees that are part of the National Science and Technology Council, which is chaired by the president. A working group of this committee, Emerging and Re-emerging Infections, was chaired by Dr. David Satcher, former Director of CDC; the group was charged with addressing emerging infectious disease issues domestically and globally from the standpoint of the 17 or more federal agencies that have some stake in this concern. The working group produced a report³ that was developed by subcommittees that focused on surveillance and response, research and training, capacity building in other countries, and emergency production and distribution of vaccines, drugs, and diagnostics. The report, which was published in the fall of 1995, served as the basis of the Presidential Decision Directive issued by President Clinton in June 1996; the directive called on federal agencies to work together with other appropriate partners to address the challenges posed by emerging infections in our global villages, including threats to our national security.⁴

What does the future hold? At this conference, some called for efforts to forecast epidemics. Others expressed concern about the impact of climate change on infectious diseases. Dr. Lederberg noted that what we really have to worry about is a major antigenic shift in influenza virus, another flu pandemic. I also worry about the gene for vancomycin resistance moving from *Enterococcus* to *Staphylococcus aureus*, giving us vancomycin-resistant *S. aureus*. Another concern is dengue in the Western Hemisphere. In 1995, the fourth of the four dengue serotypes appeared in this hemisphere; conditions are similar to those in southern Asia in the 1960s, when dengue hemorrhagic fever emerged as a major public health problem there. We also must be prepared to confront some of the "exotic" infections closer to home. Local transmission of *Plasmodium vivax* was reported recently in Houston, Texas, and, more recently, in Georgia, Florida, and Michigan. Finally, at this conference, speakers noted that peptic ulcers are often of an infectious cause. One can ask appropriately what additional chronic diseases will be found to have an infectious cause.

Apropos of the last point, the fact that antimicrobials are going to be used to treat peptic ulcer disease will increase dramatically the selective pressure provided by antimicrobial agents in this country and other countries as well. Clearly, this is a good time for the nation to strengthen its early warning system for infectious diseases.

In closing, I offer this quote from the 1992 Institute of Medicine report: "Patho-

genic microbes can be resilient, dangerous foes. Although it is impossible to predict their individual emergence in time and place, we can be confident that new microbial diseases will emerge."^{1(p.32)}

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