Emerging Problems in Infectious Diseases

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(SLIDE 1) The phrase "new and emerging infections" has become a familiar one over the past five years, the most dramatic of these infections being, of course, the now global AIDS epidemic. This epidemic is seen as part metaphor, part harbinger of a wave of troubling new infections. Among the most dramatic of these are the mysterious Ebola virus epidemics of tropical Africa with death rates of 80 to 90% and, as yet, no discernible reservoir. But there are many others such as bovine spongiform encephalitis or "mad cow disease"; the Hanta virus-induced pulmonary disease in the Americas; a new cholera variant in Asia; and the increasingly ubiquitous E. coli 0:157:H7 causing hemorrhagic diarrhea and death.

Countless newspaper articles, books, television docudramas and films have chronicled these events with varying degrees of accuracy, often with dire predictions for the future. Views expressed within the scientific community range over a broad gamut from those who express genuine concern about the future to those who assert that, in large part, we are simply detecting more unusual agents and diseases because we have better diagnostic tools.

What is reality? Should we be concerned or are accounts of these many epidemic events being exaggerated or perhaps distorted to provide better copy for science writers or special justifications for scientists to increase their research budgets? If the problems are real, why are they occurring at this particular time? What can we anticipate for the future?

Today, following my introductory overview, we will be exploring these questions in greater depth with presentations from colleagues in Taiwan, Korea, the Philippines and Thailand.

In the time available, it would be impossible to describe in any detail the many new or emergent infectious disease problems which have been identified over the past decade or so. **(SLIDE 2)** Several recently published books and monographs do this for both the scientist and the layman.[1,2,3,4,5,6] Rather, I would like first to trace briefly the events leading to the recognition of the problem and second, to highlight certain of the major social, demographic and technical changes which have a particular bearing on the ecology and epidemiology of the infectious diseases as we approach the end of this century. Finally, I would like to explore the question as to whether history can inform us as to a possible future. In brief, is there historical precedent for the occurrence of an epidemic disease which might seriously threaten the fabric of civilization as we know it?

<u>Recognition of the Problem of New and Emergent Infections</u>

Until well into the 1980s, we in the industrialized world had become increasingly complacent about the infectious diseases. Beginning in the 1940s, an emerging cornucopia of antibiotics brought victory over much of the bacterial world and new technologies, including tissue culture, brought a host of vaccines, including those to counter the most serious virus problems. At the same time, nutrition and housing standards improved. Smallpox and polio cases decreased sharply and then disappeared. Other formerly important infectious disease problems all but vanished or were able to be treated readily--measles, tetanus, rubella, diphtheria, mumps, streptococcal and pneumococcal infections, tuberculosis and others. Little progress was made in dealing with the prevalent diseases of the tropics but this was of little concern to those living in the industrialized non-tropical countries. The United States Surgeon General reflected a prevalent mood when in the late 1960s, he declared the war against infectious diseases to have effectively been won and urged that scientists turn their attention to the new frontier of the chronic diseases such as heart disease and cancer. Indeed, over the next 25 years, interest in infectious diseases waned; departments of microbiology diminished in size or vanished altogether; state and local health departments relaxed their vigilance; infectious disease residencies diminished in number; and our CDC, once the Communicable Disease Center, changed its name to the Center for Disease Control and diverted major resources to begin work in the chronic disease field.

In June 1981, a cloud appeared on the horizon. That month, the first cases of AIDS were discovered and by February 1983, the first 1000 cases had been identified.[7] The prevalent hubris that science could now readily cope with any infectious disease challenge was reflected by the then United States Secretary of Health, Education and Welfare, Margaret Heckler. She announced in April 1984 that the human immunodeficiency virus had been identified. **(SLIDE 3)** She said, "Today's discovery represents the triumph of science over a dreadful disease," and, on Dr. Robert Gallo's advice, predicted that a vaccine would be ready for testing within two years. Thirteen years later, and with research expenditures exceeding more than US$ 1000 million per year, there is as yet no vaccine. In fact, there is no vaccine even in the Phase III human field trials. There are a few drugs which at enormous cost are able to suppress virus proliferation for months to a few years and, in some cases, may even be able to eliminate the virus altogether. Whatever the case, the drugs are so costly as to be inaccessible to 95% or more of the victims of AIDS.

(Slide 4) In 1989, a more humble group of scientists met in Washington to explore the uncomfortable question as to what the prospects were for other serious disease epidemics to occur.[8] One especially disturbing scenario was raised, specifically what if HIV had acquired a gene which permitted transmission by aerosol, as influenza for example. Given the fact that the average time from initial infection to AIDS is ten years, an unprecedented incubation period for an infectious disease, those cases of AIDS first identified in June 1981 might have been but the first symptomatic victims of a massive pandemic which, by then, might well have already infected millions. As the HIV epidemic has made all too apparent, our basic understanding of microbes and pathogenesis is nowhere near adequate to be able to develop quickly either therapeutic or preventive measures in the face of a challenge, however much money is provided.

The microbial world with its countless species multiplies at astronomical rates, each species continually mutating, adapting, changing to assure its own survival. Thus, it seems reasonable to expect that from time to time, there will arise mutant forms, some highly lethal to man, with a capacity to grow and to spread readily. Of special concern are the viruses, given their need to become entangled with the genetic and metabolic machinery of host cells in order to replicate.

At that 1989 meeting, it was clear that the scenario of some sort of "Andromeda-like strain" catastrophe could not be dismissed out of hand. An in-depth review of the problem seemed indicated and thus it was decided to ask a Committee of the Institute of Medicine of the National Academy of Sciences to explore these questions at greater length. A two-year study followed and in 1992, the Committee's report was published.[1] **(SLIDE 5)** It basically endorsed the concerns of the original meeting and identified as emergent problems, 27 viruses, 17 bacteria and 10 protozoans and helminths. The Committee offered a number of important recommendations with regard to improving disease surveillance globally and for strengthening the basic infrastructure for infectious disease training and research.

Since 1992, unusually large numbers of new and emergent infections have continued to appear and some of these (such as canine parvovirus) have been able to spread rapidly and widely throughout large populations and across national borders;[9] some of these (such as Ebola) are associated with high case-fatality rates[10] and some (such as bovine spongiform encephalitis) may behave like HIV, exhibiting a very long latent incubation period before becoming symptomatic and thereby detectable.[5]

Recent Demographic, Technical and Social Changes

How might one account for this phenomenon of new and emergent diseases? What recent demographic, technical or social changes might have a significant bearing on new disease occurrence? I would cite four in particular. **(SLIDE 6)**

Population

The first and most significant force is population growth. Rapid changes are occurring, especially in terms of urbanization. **(SLIDE 7)** As recently as 1800, less than 2% of the world's population lived in urban settings; by 1950, the proportion had risen to 20%. Now, more than half live in urban areas and that number will rise to two-thirds by the year 2020. **(SLIDE 8)** Looking at this phenomenon another way, there were in 1950 only two cities with a population of 7 500 000 or more--New York and London. Today there are 30 such cities and seven, in fact, have populations larger than 15 000 000. A number of such cities are in tropical or subtropical developing countries and there, crowding, malnutrition, poor sanitation and environmental pollution are present of a nature never before witnessed in history. This is fertile soil indeed for a mutant pathogen to become established.

International travel

The second major force is international travel. Today's jetliners accommodate large numbers of travelers and at diminishingly low cost. International commerce has skyrocketed and with it, business travel. Tourism itself has become a lucrative enterprise and ever more adventuresome tourists and entrepreneurs now regularly travel into previously isolated areas. This has greatly heightened the likelihood of unusual microbes being acquired in remote habitats and transported within a day or two to other points on the globe. **(SLIDE 9)** In illustration, I would note that in the USA during the 1950s and 1960s, we had regularly recorded between 100 and 200 cases of malaria each year, all importations among tourists, businessmen or the military. During the late 1980s, the number began to increase rapidly to the point that we now record more than 1000 cases of malaria each year,[11] with small outbreaks now being observed in such as Florida, California and New Jersey among persons who have never left the United States. This is not to suggest that malaria is becoming endemic but, rather, that it represents a marker indicating the growing potential for the introduction and spread of many agents from many different areas.

Growth of hospitals

The third major adverse influence, one which may surprise you, is the proliferation of hospitals, a comparatively recent phenomenon. As we were to discover during the smallpox eradication campaign, hospitals were a common and especially dangerous site for disease transmission. In many parts of the world, hospital resources are few; isolation facilities are often ineffective or non-existent; and large numbers of friends and family regularly visit. A patient with smallpox often infected many others, persons who came from villages and towns which were many miles distant. Many times, we discovered many outbreaks of smallpox occurring over a wide area two to three weeks after hospitalization of a single case. **(SLIDE 10)** Recent experience has shown hospitals to be the primary site for epidemic transmission of measles, Llasa fever and Ebola virus disease, among others. For some diseases, this is accounted for by direct contact. In others, contaminated needles and syringes as well as other instruments are the cause because many hospitals have so few supplies that proper sterilization is impossible or, in some cases, ignored. In all hospitals, the problem of increasing antibiotic resistance is a major problem but, in fact, it is in the hospital setting where the development of antibiotic resistance principally takes place.

Industrialization and internationalization of the food supply

The fourth major influence is the industrialization and internationalization of food supplies, most notable in the industrialized countries but a universal phenomenon. This represents an unprecedented change of which few are aware. Once food was grown locally on small farms and preserved or prepared for commercial use in small establishments. If contamination occurred at any point, few were afflicted. However, economies of large-scale production dictate ever larger farms, and the capacity for processing food on an industrial scale is growing. Contamination at any point in the food production chain now can result in massive epidemics extending across many countries. **(SLIDE 11)** An illustration of this was the contamination of food with shigellosis in a United States airline food preparation kitchen. In all, 241 cases were documented; 9 000 cases were estimated to have occurred on 219 different flights going to 24 states and four foreign countries.[12] Likewise, food for processing is often obtained from many sources, mixed in processing and widely distributed. **(SLIDE 12)** The problem in the meat packing industry was illustrated by an effort made by CDC to discover the source of beef in the infamous 1993 Jack-in-the-Box E. coli O:157:H7 epidemic.[13] It was found that the contaminated lots contained beef from New Zealand, Canada and the United States. When efforts were made to trace the source from just the most likely supplier, the trail let to six states and five different slaughter houses with 443 cattle possibly responsible. Further tracing was not possible.

With fewer trade barriers and less costly transport, international commerce in food products has grown explosively. Unites States imports have doubled in the last five years and now amount to 30 billion tons annually. This includes nearly 40% of all fruit and 12% of vegetables consumed in our country. **(SLIDE 13)** And with this growth in trade has come problems: cyclospora epidemics from Guatemalan raspberries; salmonella from Ugandan and Pakistan alfalfa sprouts; cholera from Thai frozen coconut milk. The United States in turn is reported to have sent contaminated radish sprouts to Oregon and E. coli in frozen beef to Korea.[14]

Given the very diverse standards of food hygiene in our own and other countries, many have wondered that there are not many more reported food-borne outbreaks. In fact, as a recent study shows, the fact that more outbreaks are not reported has less to do with the safety of the food supply than it is a symptom of our grossly inadequate surveillance and investigation capacities. A recently conducted study by Minnesota Health Department staff concludes that food-borne disease in the United States alone accounts for 250 million cases per year and is the number one cause for visits to hospital emergency rooms.[15] The potential for disease dissemination through food is wholly different from that which existed 25 years ago--or even five or ten years ago.

<u>Historical Precedent for Catastrophic Disease Recurrence</u>

Many factors have changed and changed dramatically over recent years which would serve to facilitate the emergence and rapid spread of all manner of organisms. But how concerned should we be? After all, mankind has been around for several million years and the fact that we are here indicates than an ultimate microbial catastrophe has not yet occurred.

Thus, I turn to the concluding portion of my overview to examine the question as to whether mankind has at any time experienced an epidemic catastrophe which seriously threatened the fabric of civilization.

First, it is important to bear in mind that the opportunity for widespread dissemination of any microbial agent is comparatively recent. The risk of a major catastrophe simply did not exist until quite recently. Man was a hunter-gatherer until 10 000 years ago living in very small groups with only limited contact with others. In fact, until about 600 years ago, the world was comprised of four quite isolated geographic areas--Asia, the Americas, sub-Saharan Africa and the European-Middle Eastern states. There was little mixing of either people or microbes between the four areas. Beginning some 600 years ago, the frequency of contacts between peoples began to grow rapidly and soon, two events occurred which on one continent, seriously threatened to destroy the future of civilization as it was known and, in the second instance, decimated a population, effectively destroying the existing civilization.

(SLIDE 14)

Pneumonic plague in Europe

The first episode was pneumonic plague--the Black Death. The disease arrived in Europe from Asia in 1346 with rapidly traveling Mongol armies traversing the great silk route.[16] In just four years, plague moved north and west across Europe. Between one-third and one-half of Europe's population died. Agricultural production dropped and food shortages occurred; construction came to a halt. The plague persisted, revisiting previously infected areas sufficiently often so that the population in Europe continued to decline over the next 100 years. Not until the mid 1600s did the population of Europe regain the numbers present 300 years before. The fabric of European civilization was severely stressed although clearly it survived.

Smallpox in the Americas

A more disastrous chapter was written in the Americas with smallpox the offending organism. In 1492, at the time of the European discovery of the Americas, demographers estimated the population of native Americans to have been in the range of 70 to 75 million persons.[17] about the same as the population of all Europe excluding Russia. The native Americans had had no prior experience with a number of the infectious agents common to residents on other continents, most notably smallpox. It is presumed that smallpox emerged from an animal reservoir to become a human pathogen sometime after the first agricultural settlements, some 10 000 years ago. Only then were there adequate numbers of humans in sufficient continuing contact to permit this uniquely human infection to sustain itself by continuing person to person spread. By the time smallpox had emerged, nomadic Asian tribes would have already crossed the land bridge to North America.

The Spaniards brought smallpox to the Americas soon after the first settlements were established on Hispaniola, and so devastating was the disease that the resident native population all but vanished within a few years. Needing slaves to work the fields, Cortez was dispatched to Mexico with an army of fewer than 500 men whose object was not conquest but to capture slaves. Inadvertently, he brought with him, smallpox. Massive epidemics ensued of such catastrophic proportions as to result in the collapse of the Aztec civilization. Subsequently, smallpox spread south through the Andes and the Incan empire wreaking yet more havoc. One observer in Peru wrote: **(SLIDE 15)**

> "They died by scores and thousands. Villages were depopulated. Corpses were scattered over the fields or piled up in the houses or huts. All branches of industrial activity were paralyzed. The fields were uncultivated; the herds rove untended; and the workshops and mines were without laborers. It was only with difficulty that the ships could be manned. (Some) escaped the foul disease, but only to be wasted by famine."[18]

It is estimated that over the first 75 years after contact with Europeans, the American Indian population declined by between 75 and 90%.

The devastation in North America was equally severe, depopulating vast areas of the country. A report in 1838 states: **(SLIDE 16)**

> "We have, from the trading posts on the western frontier of the Missouri, the most frightful accounts of the ravages of smallpox among the Indians....The number of victims within a few months is estimated at 30 000 and the pestilence is spreading....The vast preparations for the protection of the western frontier are superfluous. Every thought of war (has been) dispelled....No language can picture the scene of desolation which this country presents."[19]

Thus, there is precedent within the era of written history for the occurrence of a disease so severe, so transmissible as to effectively destroy the fabric of a civilization. It is interesting to note in passing, that smallpox is but one of a family of poxviruses. Another member of that family is myxomatosis, a rabbit virus which proved to be especially lethal to the European hare. Myxomatosis, introduced into Australia to control the population of European hares, killed 99.8% of all animals infected.

Conclusion

We tend to forget how serious infectious diseases can be. To put this into perspective, it has been estimated that during this century, between 100 and 150 million persons died either directly or indirectly from armed combat or, on average, one to 1.5 million persons per year. This is substantially fewer deaths than were caused by smallpox each year as recently as 1967 and fewer deaths than are now caused by either tuberculosis or malaria.

As never before in history, I believe we must take seriously the threats posed by new and emerging infections. We need to strengthen greatly our capacity for surveillance to detect disease and for specialists in infectious diseases, epidemiology and immunology to be prepared to combat them.

Clearly, we are prepared to expend vast sums of money in armament to protect ourselves from armed conflict. We have not yet recognized, however, that microbes pose a far more serious threat to our survival. I paraphrase Dr. Josh Lederberg, the Nobel laureate, who stated **(SLIDE 17)** that it is clear that man's only competition for the dominion of the planet are the viruses--and the ultimate outcome is by no means fore-ordained.[20]

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