Controlling Infectious Diseases

by Stephen S. Morse

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Long believed to be all but conquered, infectious diseases have returned with a vengeance. They have included not only deadly outbreaks of Ebola in Africa and the worldwide AIDS epidemic but also Lyme disease, cholera, new strains of influenza, and hantavirus pulmonary syndrome, which causes death from respiratory failure in over half the people infected. Yet despite much talk about "new" diseases, most are anything but. One category of worrisome microbes, including those that cause antibiotic-resistant tuberculosis, are just hardy strains of well-known bacteria: when antibiotics are used inappropriately, they kill only the weaker individuals, allowing hardy strains to flourish. And some of the most feared infections, like AIDS, derive from viruses that have simply moved into new areas or acquired new hosts. Many are zoonotic, meaning that they come from animals, and they often appear as a result of ecological changes. Frequently human activities are at the root--clearing forests or cultivating land, for example, can disturb the habitats of sequestered natural hosts such as mice and mosquitoes, increasing their contact with humans.

As those activities have accelerated, the incidence of emerging zoonotic infections has grown with them.

Unfortunately, too, infections are more likely than ever to reach vast numbers of people. Historically, diseases have come as byproducts of exploration, trade, or warfare, when the movement of people, animals, or goods brought geographically isolated infections to new grounds. Rats carrying bubonic plague first entered Europe by the overland route from central Asia, through war, the silk trade, or both. Most historians believe the mosquitoes that carry yellow fever were spread from West Africa to the New World by ships plying the slave trade. Today, trucks and airplanes have largely replaced the slower-moving caravans and steamships, creating much richer opportunities for infections.

Moreover, economic conditions in many parts of the world are encouraging the mass movement of workers to cities. Thus, infections that may once have remained obscure in rural areas are likely to reach large populations. And in industrialized countries, high-density settings such as daycare centers can allow diseases to spread rapidly once they have gained a foothold.

These are global problems transcending political and national boundaries. An infection may come to light anywhere in the world and span continents within days or weeks. Recognizing as much, several expert groups, including the Committee on Emerging Microbial Threats to Health at the Institute of Medicine of the National Academy of Sciences, have concluded that a surveillance system to spot emerging infections--an "early warning system"--is an essential first line of defense. But so far we aren't even close to having such a system.

To be sure, some steps have been taken. Several national governments and some major U.S. agencies including the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) have joined with WHO to begin formulating international action plans. In May 1995 the World Health Assembly, the governing body of WHO, approved a resolution to make surveillance of emerging and re-emerging infections a priority. Later that year, proposals for streamlining surveillance efforts and for a coordinating group were implemented in a "first steps" mode. All these initiatives are excellent and deserve enthusiastic support. But because they will require resources, political will, and sustained commitment, achieving their goals will be a challenge.

An early warning system requires three elements at the front line. Recognition of "new" clinical syndromes is the first: there has to be a way to identify patients with such syndromes and gain access to them for further studies. The second requirement is resources for epidemiologic field investigation--the medical detective work that helps determine the source of infection and the mode of transmission--and the third is laboratory diagnosis, a vital adjunct to the other two. By running tests on the materials like blood and sputum that clinicians take from patients, labs help differentiate new infections from common ones and estimate their extent and frequency; by running tests on potentially infected materials collected in the field, labs are also key in determining the source of infection and the mode of transmission. Depending on what is found, the next step may by immediate action to limit the spread of infection, perhaps through controlling mosquitoes or rodents, protecting the water supply, or administering immunizations or anti-microbial agents. But one of the main problems right now is that this stage is often not even reached because of deficiencies in the surveillance system. The clinical, epidemiological, and laboratory components need to be much better integrated, and in particular epidemiological expertise and laboratory resources are seriously lacking.

Even so, the concerted efforts of the people and agencies in the system have provided enough examples of good ad hoc responses to outbreaks to prove that we need not be defenseless before an onslaught of infectious disease. For instance, consider the outbreak of hantavirus pulmonary syndrome in the summer of 1993. Beginning in May of that year, patients were admitted to hospitals in New Mexico, Arizona, and Colorado with fever and acute respiratory distress; more than half died. By mid-August, there would be 23 cases in the three states. But there could have been many more: the public health system had happened to work well in this situation.

The first stroke of luck was that the outbreak was spotted fairly early in its course: an alert clinician in New Mexico noted that two of his patients seemed to be stricken with the same inexplicable disease, and a follow-up on his observation led to identifying several other cases. This prompted him to contact the state health department, which also responded swiftly. When investigations confirmed that there was indeed a cluster of unusual disease, officials requested assistance from CDC.

Any outbreak with a high rate of mortality is taken with the utmost seriousness, and CDC mounted what it called a "full-court press," mustering all available resources to send a team rather than the usual lone epidemiologist to the Southwest. Meanwhile, a growing group provided laboratory support back in Atlanta at CDC headquarters, receiving materials from the team and testing them for a wide variety of infectious agents. When the tests suggested that a previously unrecognized hantavirus, a type of rodent infection, was the culprit, attention immediately turned to trapping local rodents for further laboratory testing. Researchers soon succeeded in identifying the host--the common deer mouse--and plans for controlling rodents and teaching local residents how to avoid contact with them got under way.

One reason the current system seldom works this well is that responsibilities are too broadly diffused. The task of disease surveillance and control in the United States rests with each state, and the attention given to it therefore varies according to local needs and resources. As the main federal agency for epidemiology and disease prevention, CDC maintains liaison officers in many state health departments and is available on request to help identify, investigate, or confirm cases, but these actions must be initiated at the state level. Even the list of diseases that must be reported to the state health department by physicians and local officials is determined by an organization of state public health officers; although nationwide consensus exists on most of the diseases, there are some variations from state to state, and it is hard to make additions to the list.

Under these conditions, infections are often identified as much by luck as by intention. For instance, an outbreak of hemolytic uremic syndrome, an illness characterized by bloody diarrhea and serious kidney disease and caused by a strain of *Escherichia coli* bacteria in hamburger meat, was missed in Nevada, and probably other states, before it was identified in 1993 by Washington state public health officials. No wonder that in 1994, when CDC set goals for the fight against emerging infections, it included strengthening the public health infrastructure not only at the federal level but also at the local and state level. No wonder, too, that meeting this goal was cited as key to meeting other goals, such as improving surveillance and control programs.

On the global level the situation is the same writ large. WHO, the world's public health agency, is in a similar position internationally to CDC domestically, responsible for collecting information and coordinating activities. In other words, the organization is dependent on the cooperation and support of its member countries, whose health budgets are often limited. To make matters worse, funds for infectious-disease surveillance at WHO itself are limited--the agency has no money to carry out new initiatives. And WHO is fragmented, with several different units responsible for different kinds of surveillance data. For example, a number of important infectious diseases are foodborne and waterborne, but authority for these lies with separate offices within WHO.

An international system that would respond to novel infections worldwide as effectively as CDC responded to hantavirus pulmonary syndrome in New Mexico is not at all impossible to imagine. One could be organized through local or regional centers, each of which integrates clinical, epidemiological, and laboratory expertise. Such centers would work with national governments to develop local surveillance networks consisting of area hospitals and health workers trained to detect unusual and dangerous clinical syndromes, and they would strengthen these networks by building a broad base of support within the region. Toward that end, they would forge good working relationships with public health authorities and medical schools to tap specialized expertise when needed, and cooperate closely with government agencies, volunteer groups, and other organizations committed to safeguarding public health. The networks would also have access to a back-up system of more comprehensive laboratories. A central hub would receive surveillance information from around the world, coordinate the work and reporting of the individual centers, and organize an appropriate response to emergency situations.

Some components of such a system are already in place, and indeed, it seems logical, as WHO has suggested, to begin by strengthening and better coordinating existing resources. WHO itself might serve as the central hub of the system, tracking both human and zoonotic diseases, the latter in partnership with the International Office of Epizootics (OIE), which currently handles outbreaks of diseases among animals. Prominent among the other resources at hand is the network of WHO Arboviruses and Hemorrhagic Fevers Collaborating Centers, which have specialized in unusual infections (arboviruses, transmitted by mosquitoes and other arthropods, are responsible for diseases such as yellow fever and dengue, and hemorrhagic fevers are those like Ebola that involve massive bleeding). But beyond that, we actually know very little about what we have to work with, so the next step would be to conduct a more comprehensive inventory and assessment of resources worldwide.

Once this has been accomplished, we could designate from among the existing facilities the dozen or so regional centers that would bring together clinical, epidemiological, and laboratory expertise. These centers would be looking for clusters of unexpected and unexplained deaths. To prevent their mission from becoming too diffuse, they could concentrate at first on a small number of key syndromes characteristic of some particularly serious emerging infections, like severe or fatal acute respiratory disease and severe acute neurological disease. Such syndromes are especially worth noting in adults, who can be assumed to have developed immunity to their more common causes. Antibiotic-resistant bacteria would be a priority as well.

After this skeletal network is functioning, WHO, in conjunction with the governments of its member countries, should expand it to include other types of diseases. The geographic base should be broadened as well; this would require identifying additional facilities that already meet some of the necessary criteria and could readily be upgraded. Priority should be given to facilities in areas of high biodiversity undergoing major ecological or demographic changes. After all, since many emerging infections are zoonotic in origin--and since they often arise when natural habitats are disrupted and spread when people move from one place to another--such areas are likely to be hot spots. The Ebola virus and quite possibly HIV originated in Africa, one of the most biologically diverse places on the planet.

D.A. Henderson, who spearheaded the successful smallpox eradication program at WHO, recommended "look out" centers in the expanding urban areas on the periphery of tropical cities. Important port cities and other major places of high population density and flux should also be targeted. Another sensible action would be to include health surveillance in the plans for major projects such as irrigation, road building, and land clearance, especially in areas of high biodiversity. In the longer run, broader surveillance of ecological changes that might presage an increase in natural hosts for disease could also be considered.

Once in place, an early warning system for emerging infections would need good communications. As anyone who has tried to make a phone call in an emergency will attest, the importance of communications cannot be overemphasized. Fortunately, however, the technologies to establish good communications exist; the problem is chiefly one of ensuring that all the people who need them have access to them and know how to work them and who to contact. Fax machines have proved invaluable, delivering vital documents across the miles in just a few instants. And in the near future, technologies such as electronic mail will play a crucial role, allowing for an almost immediate international response to health emergencies.

Another computer innovation of note--WHONET--is software developed by physician Thomas O'Brien's group at Brigham and Women's Hospital in Boston. WHONET has been designed for dealing with antibiotic-resistant bacteria. Such pathogens can often be identified without much difficulty even in small hospitals with relatively unsophisticated laboratories; the challenge is not so much diagnosis as information gathering to spot trends. The sooner clinicians and public health officials can be advised of a resistant strain of bacteria, the sooner they can start working on a strategy to contain it.

With that in mind, O'Brien's group made the heart of WHONET a program that can be used on a small desktop computer in a microbiology laboratory to both handle recordkeeping and tabulate the results from routine tests of bacterial sensitivity to antibiotics. Participating labs agree to compile and send information periodically to a centralized facility for trend-spotting analysis.

Improved laboratory diagnosis is crucial, too, and here biotechnology researchers have helped by developing efficient new methods, although the resources to make effective use of those methods are often lacking. For example, diagnosing viral infections can be tricky, but in the case of those viruses that have been identified, it can be routine now, thanks to advances such as ELISA, or "enzyme-linked immunosorbent assay." In these tests, material such as blood from a person who might be infected is typically exposed to components of a virus or other infecting agent to see if the body has manufactured proteins called antibodies to combat that agent. If the body has indeed manufactured the proteins, the person is determined to have been infected. Also, polymerase chain reaction technology (PCR), which allows large quantities of DNA to be synthesized from a single molecule, detects viruses with exquisite sensitivity. Not only are tests like ELISA and PCR rapid and reliable; they can be made widely available as well, since the needed compounds can frequently be supplied in quantity and in a stable, standardized form.

But while such technologies offer a great deal of hope, there is no substitute for skilled, dedicated people, and today those people are in short supply. One difficulty is that opportunities are limited. People are unlikely to enter any field if they suspect that no job will be waiting for them. A career path must therefore be assured, which is an important reason why the proposed system needs to be established. Training might occur through supervised field work and perhaps personnel exchanges between different facilities in the system.

Lack of qualified personnel is perhaps most serious in the area of field epidemiology. Experts are few and largely of advanced age, raising the question of how effectively their know-how will be transmitted to future generations. And the fact is that field epidemiology is essential. Clearly, if the source of an infection and the mode of transmission remain unknown, the information traversing even the most extensive early warning system will be severely limited. Moreover, the immediate response to any outbreak, as well as the control programs to follow, would need to build on the data and contacts amassed during the investigative phase.

In the United States, the traditional mechanism for training people in epidemiological investigation is the CDC's Epidemic Intelligence Service (EIS), which has worked well. As part of their on-the-job training, EIS officers provide liaison services with state health departments or are sent out on field investigations. CDC has also developed an international version, the Field Epidemiology Training Programs, but while this is a good model, only about a half-dozen countries have programs now, and funds and personnel for expansion are limited.

Besides setting up an early warning system, a long-term strategy to counter emerging infections would mean taking a critical look at the ways we address the issues of prevention and control and developing a response system to improve on the current ad hoc approach. An effective response system would include advance plans for a range of contingencies, and would be integrated with the surveillance system, activated by the information that surveillance supplies and using many of the same lines of communication. Indeed, surveillance and response might be seen as two halves of the same process. And just as strengthening the surveillance system will require streamlining and coordinating available resources, so, too, will strengthening the response system.

Another clear need is better methods of health education--for example, because antibiotic-resistant bacteria evolve through improper administration of antibiotics, education of antibiotic prescribers and users is critical. With other problems, better understanding of how to motivate health-promoting behavior such as safer sex is more to the point. And that might be best accomplished by extending the public health infrastructure to draw on research in the social sciences, which might also help us understand migration patterns and other human factors that contribute to the spread of disease. Finally, continuing basic research on pathogens and immunology must be encouraged, along with research on potential zoonotic threats and on ways to quickly and inexpensively develop vaccines.

Since the public health infrastructure in most of the world is fairly rudimentary and thus unable to absorb large investments anyway, the initial costs of implementing the international components of an early warning and response system for infectious diseases could be modest--as little as $10 or 20 million a year. Many of those funds could come from pooling together the resources of different countries; the rest could come from private donors that have contributed to public health programs in the past--for example, the World Bank, development agencies, and major foundations. The money would finance upgraded resources at a dozen or so locations, supplying computers, software, and telephone or satellite links to ensure reliable data gathering and communications. It would provide for some personnel training, annual meetings of consortium members, and a small central staff as well.

But most important, the commitment, and the financing, must be sustained as the public health infrastructure grows larger, and that will certainly not be so cheap. Also, the few countries in which a large public health infrastructure has already been established will require more resources early on, as their job will be to maintain and improve those systems. The United States, in particular, needs substantial backing if we are to bring our infrastructure up to the levels we expect. As a start, a working group on emerging and re-emerging infectious diseases set up by the Committee on International Science, Engineering, and Technology of the National Science and Technology Council has made some excellent recommendations. Among them is the idea that a number of U.S. government agencies could each contribute a small portion of their funds to a coordinated effort carried out by an interagency task force.

Granted, developing the political will to follow through on such initiatives is especially difficult in this age of shrinking resources and multiple demands. Still, history shows that failing to respond to infectious diseases carries a heavy price. Who could have imagined the enormous savings to be realized if HIV had been found and stopped early? In 1993, the World Development Report, the annual report of the World Bank, noted that in the previous year alone, industrialized countries paid $4.7 billion to care for AIDS patients.

As of now, humanity remains vulnerable to a staggering array of infections. We have no unified system for global surveillance, let alone one for response. Some of us have been paralyzed by complacency--thinking, wrongly, that the threat of infectious diseases is past. Others have been equally paralyzed by defeatism, perhaps feeling that it is too difficult to build the systems needed to protect us. But even imperfect systems are better than none at all--and given today's urgent needs and the even greater needs we are likely to face in the future, there is more harm in delay.

> [This article, which first appeared in the October 1995 issue of the MIT journal, *Technology Review*, has been edited for this space. Discussion of the FAS ProMED project has been omitted, since the information is available on these pages. The article is published here with the permission of the MIT editors and the author.]

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