
Global Monitoring of Emerging Diseases: Design for a Demonstration Program

*Stephen S. Morse, Barbara Hatch Rosenberg and Jack Woodall
for the ProMED Steering Committee*

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Abstract

The emergence and reemergence of infectious diseases as the result of recent and ongoing social and environmental changes urgently calls for a global surveillance system, so that unusual outbreaks can be recognized and controlled at an early stage. ProMED, a project of the Federation of American Scientists, proposes a demonstration program which would prioritize a small number of strategically located institutions in the developing world, mainly those least in need of upgrading, for development as Sentinel Centers. Each of these Centers would develop its own local/regional network with which it would exchange information and assistance, and through which it would collect clinical data and specimens for monitoring the emergence of a limited number of defined syndromes. In this way a functional, although limited, at minimal cost. The network would serve as an experimental model for future expansion. A central Program Office would provide protocols, assistance, training, quality assurance, communications, etc. and would coordinate fundraising and program activities. If successful, the syndromes monitored would be expanded and additional institutions strengthened to become new network centers.

INTRODUCTION

History of the Proposal

At a conference in 1993 convened in Geneva by the Federation of American Scientists, and co-sponsored by the World Health Organization, 60 prominent health experts from all parts of the world rallied to the idea of a global program for monitoring emerging infectious diseases and unanimously called on the ProMED Steering Committee "to take action to assure the design,

promotion, and implementation of such a program."

The process continued at subsequent meetings, consultations and through mailings. A World Bank official encouraged and guided the drafting of a proposal, which was circulated in early 1996 for comment to more than 300 experts around the world, including all those who had participated in ProMED activities. This document, a May 1996 revision of the draft proposal, incorporates many of the suggestions made by these reviewers but does not necessarily reflect specific endorsement of every aspect of the plan by every participant.

ProMED proposes a research program to demonstrate the feasibility of a network of centers to monitor emerging diseases directly through surveillance for selected syndromes, coupled with effective laboratory backup. With financial resources in short supply, a small network of strategically located sentinel centers with capability for surveillance of both endemic and emerging diseases may be the most effective way, in the near term, not only to test the concept but to begin providing early warning of serious epidemics.

The Need for a Global Program

Numerous recent episodes of emerging and reemerging infections, including the global AIDS pandemic, the continuing spread of dengue viruses, the now-frequent appearance of hitherto unrecognized diseases such as the hemorrhagic fevers, the resurgence of old scourges like tuberculosis and cholera in new, more severe forms, and the economic and environmental dangers of similar occurrences in animals and plants, attest to our continuing vulnerability to infectious diseases throughout the world. There is reason to believe that the number and incidence of emerging diseases and the risk of reemerging diseases are all increasing. Factors responsible for the increase include such social changes as mass population movements, rural-to-urban migration and accelerated urbanization, population growth, rapid transport, global trade, new food technologies, and new life styles as well as environmental changes that increase the risk of human exposure to zoonotic or vector-borne infections, such as altered land use patterns and irrigation.

These are global problems. A new infection may first come to light in a circumscribed area, but in suitable circumstances the infection can span entire continents within days or weeks, as influenza periodically demonstrates.

Many experts, both within and outside governments, have warned of the need to improve capabilities for dealing with emerging infectious diseases. Invariably, a primary recommendation has been the development of an effective, worldwide infectious disease surveillance system (see, for example, the seminal U.S. Institute of Medicine report, *Emerging Infections: Microbial Threats to Health in the United States*, issued in 1992). A global program aimed at recognizing unusual outbreaks at an early stage, in order to prevent their spread, would pay enormous dividends for the entire world as well as for the immediately affected

areas.

There is presently no functional system anywhere for monitoring emerging diseases. Current surveillance capabilities are fragmentary, lack coordination, and are geared toward established diseases. Moreover, they have mostly fallen into neglect. This is true both at the national level and internationally. The title of an article in *Science* (April 15, 1994) by experts at the U.S. Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) has summed up the situation very well: "Infectious Disease Surveillance: A Crumbling Foundation."

Recent Responses

In response to the urgent need for new initiatives in this field, a conference on Emerging Viruses, held in 1989 in Washington, D.C., led to the U.S. Institute of Medicine study on *Emerging Infections*, completed in 1992. Soon thereafter, ProMED, an international non-governmental project, was organized by the Federation of American Scientists to promote the establishment of a global Program to Monitor Emerging Diseases. The project was launched at a conference (co-sponsored by WHO) in 1993. ProMED has endeavored to forge effective partnerships among front-line health professionals around the world in order to lay the groundwork for a sustainable program that will be relevant to both local and global requirements. This proposal, based on input from distinguished infectious disease experts from some 40 countries and every region of the globe, is an outcome of that effort.

Also in 1993, the World Bank devoted its World Development Report to *Investing in Health*. In a related 1993 World Bank publication, *Disease Control Priorities in Developing Countries* (ed. Jamison et al), epidemiological surveillance is cited as one of four capabilities that are critically needed in order to design effective disease control strategies, one that, in most developing countries, needs to be greatly strengthened.

In August 1994, the project began operating ProMED-mail, an electronic conference for reporting on emerging diseases. With funds provided to FAS through grants, the conference was implemented by SatelLife (a non-profit health communications subsidiary of the Nobel Prize-winning International Physicians for the Prevention of Nuclear War). It quickly demonstrated the value of a direct mechanism for rapid exchange of up-to-the-minute news from any source on emerging diseases of all species. With more than 6000 participants in over 125 countries, as of September 1996, ProMED-mail is being reorganized in collaboration with SatelLife to become a permanent, independent global reporting system.

Recently there has been an encouraging upsurge in national and regional planning for surveillance of emerging diseases, but there is as yet no global program. In Europe, the Salm-Net system has been established for surveillance of bacterial diseases. Canada is beginning to

implement a new national plan for surveillance and response to emerging diseases, including coordinated research, emphasis on rapid communications, and an interest in international collaboration.

In the United States, the CDC's plan for domestic surveillance as outlined in *Addressing Emerging Infectious Disease Threats: A Prevention Strategy for the U.S.* (1994) cites the importance of international surveillance for U.S. health and proposes the establishment of a global consortium of centers for the detection, monitoring and investigation of emerging infections, and the establishment of an information exchange system linking public health agencies in different countries. In 1995, a U.S. interagency Working Group on Emerging and Reemerging Infectious Diseases issued a report entitled *Global Microbial Threats in the 1990s*, which recommends a variety of U.S. actions to promote the development of an international partnership to address emerging infectious diseases.

The European Union has developed a Communicable Disease Surveillance and Prevention Charter that includes proposals for collaborative action, and funds have been provided to take the process forward in the future. A Joint EU-US Action Plan, signed in December, 1995, set up a task force "to develop and implement an effective global early warning system and response network for new and reemerging communicable diseases, such as AIDS and the Ebola virus."

PAHO, the Pan-American Health Organization, held a workshop in June 1995 on "Combating Emerging Infectious Diseases: Challenges for the Americas" to shape a regional strategy for prevention and control. They plan to strengthen and link established laboratories and surveillance facilities, and to develop a system of regional and subregional reference laboratories, aimed at regional self-sufficiency in diagnostics. Regional conferences on emerging diseases have also been held in Thailand, and by the South-East Asia and Eastern Mediterranean WHO regional offices; others are in the planning stages.

The Director-General of WHO issued a report on emerging diseases in January 1995. A related resolution, passed by the World Health Assembly in May of that year, requested the Director-General to establish strategies to improve recognition and response to new, emerging and reemerging infectious diseases. As a result, in October 1995, WHO reorganized to establish a Division of Emerging and Other Communicable Diseases Surveillance and Control (EMC) . During 1996-7, the Division plans to take a number of steps to strengthen existing laboratory-based surveillance systems for the specific diseases within its mandate and to enhance rapid epidemic response under WHO auspices (*EMC Summary of Programme Activities and Budget, 1996-1997*). EMC's role will be essentially to serve as a nerve center to facilitate and coordinate existing programs and activities, mostly outside WHO, and to encourage national capacity-building for strengthening national and regional infectious disease surveillance and response capabilities (*EMC Draft Strategic Plan Outline, 1996-2000*).

In January 1996, 36 medical journals worldwide each devoted an entire issue to emerging and reemerging global microbial threats. Over 200 articles document the occurrence, causes, and consequences of these diseases, leading the *Journal of the American Medical Association (JAMA)* to conclude that "world health is indivisible, that we cannot satisfy our most parochial needs without attending to the health conditions of all the globe. ... We have never been more vulnerable; this vulnerability must be matched against the extraordinary sophistication of the science that we are, in principle, able to pit against the threats." The first need is for "concerted global and domestic surveillance and diagnosis of disease outbreaks and endemic occurrence. This must entail the installation of sophisticated laboratory capabilities at many centers now lacking them." But in spite of the urgency of the situation and the widespread planning activity described above, "tangible responses by government in the form of budgetary or staffing commitments remain negligible." (Quotations from editorial by Joshua Lederberg, *JAMA*, vol. 275, pp 243-5).

Media coverage and public awareness of emerging diseases have grown rapidly as the result of recent outbreaks, scientific conferences, and popular books and films (in the United States, for example, Richard Preston's *The Hot Zone*; Laurie Garrett's *The Coming Plague*; Robin Cook's *Contagion*; the movie "Outbreak"; and many TV specials).

In sum, there is now much interest in monitoring emerging diseases, but very little substantive action. However, the momentum evident in the public, scientific and governmental sectors makes this the right time to undertake a practical program.

Overview: Outline for a Demonstration Program

Given the current dearth of resources and the limitations on WHO/EMC, what can be foreseen as things stand is a painfully slow evolution of disparate elements toward a unified global system for monitoring emerging diseases. For more rapid progress, significant investment will be needed in developing relevant capabilities in institutions in the developing world, particularly in environments where diseases are most likely to emerge. We propose making a modest start in this direction by prioritizing a small number of strategically distributed institutions, mainly those least in need of upgrading, for development as sentinel Centers. In this way, a functional, although limited, network could be rapidly established at minimal cost. The system would serve as an experimental model program for future expansion.

The Centers would start by monitoring the emergence of a limited number of defined syndromes, through broadly-based local clinical outreach. Each Center would develop laboratory capabilities for identifying the likely agents for the targeted syndromes, as well as for the well-known cosmopolitan and locally-endemic diseases. In developing countries the latter will generally overshadow emerging diseases and will therefore be the main focus of concern and the incentive for undertaking the program.

The goal would be to achieve full competence at each Center within, at most, five years, and then begin to expand the number of syndromes monitored. If successful, the number of Centers could also be increased, as resources permit, to cover more areas of the world.

Concentration on a small number of strategically located medical facilities in developing countries to create comprehensive centers of excellence would establish regional nuclei in areas critical for monitoring emerging diseases, without waiting for universal progress. The Centers would reach out to other institutions in their regions, providing medical information and training. This would boost regional interest and confidence, and thereby encourage further expansion of local capabilities for combating infectious disease.

The ProMED plan calls for the formation of a network consisting of, roughly, ten of the most adequately prepared medical facilities in different regions of the developing world. To gain experience for future expansion, at least one of these should, if possible, include coverage of animal diseases. A Center might consist of a group of nearby, closely-collaborating institutions. Criteria for the Network Centers. Agreement and cooperation of the government would be essential, in each case. Each Center would develop its own local/regional network including clinics, hospitals, health care providers, academic centers, government agencies and voluntary organizations with which it would cooperate and exchange information. The Centers would collect clinical data and diagnostic samples with the help of these regional networks. The Centers and their networks would be assisted in developing expertise in recognition and diagnosis of the specified syndromes, and would have access to designated specialized reference laboratories.

The process would be coordinated by a Program Office, which could be located at one of the Centers or at a separate location. This office, in collaboration with various programs at WHO, would maintain the network's level of competence through a quality assurance program, and provide diagnostic materials and equipment where needed, training activities, and regular meetings. The office would also solicit and help to raise financial support for individual Centers to cover other needs. The Centers would be linked to the Program Office by an electronic communications system, through which surveillance information would be reported in a timely manner and relayed to alert other Centers and interested institutions.

The network would coordinate with existing networks such as WHONET (a global reporting system for antibiotic resistance) and other WHO electronic reporting systems that may be established, with the goal of forming a unified global communications system on infectious disease surveillance that will incorporate data from existing and future international, regional, national, and local surveillance efforts.

Because of their common interest in zoonotic diseases and the similarity of infectious diseases in humans and animals, many human and animal disease experts believe that collaboration in a

surveillance program would be beneficial to both and would eventually provide greater efficiency and decreased costs. Diseases of animals and plants, as well as those of humans, affect human health and well-being; they contribute to malnutrition, a factor in human vulnerability to infectious diseases, and are subject to similar factors determining emergence. A unified monitoring program would ultimately provide valuable feedback among specialists. However, the initial program described in this plan deals only with human disease. ProMED is developing a separate plan for monitoring emerging plant diseases. And the ProMED AHEAD (Animal Health/Emerging Animal Diseases) project is exploring the feasibility of a pilot program in sub-Saharan Africa.

WHO's important global mandate may make it difficult to incorporate a limited, trial program, especially in view of current resource limitations. A demonstration program could be established outside WHO as a research project which, if successful, would eventually expand and merge with other surveillance activities at WHO. Alternatively, the program could be established as a cosponsored Special Program under WHO, with the expectation of future expansion to become a comprehensive system. In either case, the program would provide a bona fide attack on emerging diseases and it would serve as a laboratory for developing surveillance strategies. A Possible Organizational Framework

The demonstration program proposed here is designed to complement current and planned national and regional surveillance activities and the disease-specific programs conducted by WHO, and to avoid unproductive redundancy.

Additional Benefits

In addition to testing procedures and feasibility, the limited program proposed would strengthen regional capabilities for monitoring and combating all infectious disease. Early warning of outbreaks in the areas covered by the Centers would make it possible to utilize available global resources more effectively. When assistance is needed to control an outbreak, aid would be sought and facilitated by the program office, in cooperation with appropriate WHO programs. Although the program is not designed to develop response capabilities, it would catalyze and promote national and regional activities to control infectious diseases in the areas where the Centers are located.

Ultimately, the program's surveillance information would be invaluable in setting priorities for technology transfer and for research and development of diagnostic technology, drugs, antisera, vaccines and other responses to control outbreaks. A long-term goal would be to develop this kind of applied research at the Centers, to make them comprehensive centers of excellence in the field of infectious diseases.

Surveillance information would also be of value to programs such as the WHO Special Program for Research and Training in Tropical Diseases (TDR), the Tropical Medicine

Research Centers (TMRC) and the International Collaborations in Infectious Disease Research (ICIDR) programs at the U.S. National Institute of Allergy and Infectious Diseases, the Pacific Basin Respiratory Virus Research Group now under development in Australia, the WHO Global Program for Vaccines, the Essential National Health Research (ENHR) networks of the Council on Health Research for Development (COHRED), and the recently proposed Program for Controlling Emerging Infectious Diseases (ProCEID, a non-governmental initiative to seek establishment of an international program to develop diagnostics, vaccines and antisera for emerging diseases).

The program's surveillance and diagnostic information would be expected to stimulate the development of treatment and prevention strategies and emergency response planning. The development of new options for medical intervention would, in turn, enhance the value of the surveillance program.

Linkage of surveillance information on emerging diseases with environmental and climate research programs and geographical information systems might make it possible to foresee times and places where problems may arise in the future, as well as to better understand the reservoirs of disease and the ecological dynamics involved in the emergence, resurgence and redistribution of pathogens and vectors. It is well known that environmental sources of microbial pathogens, including insect, rodent, and algal populations that may carry disease, often respond rapidly to environmental changes.

2. INITIAL OBJECTIVES OF THE PROGRAM

The primary objective proposed for the initial program is to recognize and provide early warning of outbreaks of certain distinctive and easily recognized clinical syndromes in order to alert response to prevent the spread of "new" pathogens or the reemergence of known pathogens on an epidemic scale. The program will test the feasibility of this approach.

Syndrome surveillance based on clinical case definitions as the starting point has been advocated by a number of colleagues. Indeed, two major surveillance systems, one for acute flaccid paralysis (under the polio eradication program), and the other for fever with rash (under the measles program), use this model. This approach has also been used successfully for meningococcal meningitis, and experience under the CDC/USAID "Data for Decision Making" program with several other diseases, including cholera and yellow fever in addition to meningitis, indicates that the approach is workable and can be a cost-effective complement to laboratory-based systems. This approach has been chosen because it may allow the recognition of emerging infections caused by presently unknown etiological agents when reference laboratories cannot immediately identify the agent. However, laboratory work-up of cases, and access to a system of laboratories to identify known agents, are also essential parts of the

program.

Active surveillance for the specified conditions would be carried out by the network of strategically-situated Centers that would recognize, investigate, identify and report cases of the target syndromes in their regions, using a clinical and referral base developed by each Center. Coordination and supporting services, including access to reference laboratories, would be provided by a central program office linked to the Centers by an electronic rapid communications system supplemented by fax backup. Reports from the Centers would be analyzed and circulated to other Network Centers and to relevant agencies as an early warning of the possible emergence of the observed diseases and as an alert or call for aid, when needed, to contain their spread.

In the operation of the program, several considerations, in addition to national commitment, will be paramount: clearly defined objectives, simplicity of operation, development of a broad local base, and adequate support to the network from a central office and other sources in order to build capacity. In its initial phase the program would establish network procedures according to these principles and would strive to develop a sense of partnership among network participants.

Thus, unlike most surveillance systems, which tend to be centrally run with a hierarchical (vertical) structure, the program is designed to be strongly horizontal, with emphasis on building area networks and local partnerships. **An important objective of the program is to strengthen and deepen local involvement and build capacity, particularly with respect to clinical and laboratory diagnostic and epidemiological competence.** In the long run, an effective global program will require a network of essentially self-sufficient Centers, each with extensive regional outreach and capability for a variety of responses to control outbreaks.

As the program proves itself, other facilities and their governments would be encouraged to strengthen their capabilities in order to become members of an expanded network. **The initial program would test the implementation of a surveillance system for emerging diseases and the degree of cooperation that could be achieved.** If successful, the number of syndromes surveyed and the size of the network could be increased.

Disease Syndromes Suggested for Surveillance in the First Phase of the Program

1. Unexplained severe acute respiratory distress syndrome (ARDS): severe or fatal cases with fever (temperature $>38.3^{\circ}\text{C}$) in humans, age >5 and <65 ;
Signs <1 wk duration;
Acute respiratory distress or bilateral pulmonary infiltrates within 1 week following hospitalization;
Noncardiogenic;

- No immediately identifiable specific cause.
2. Encephalitis/meningitis in humans over 5 years old;
Signs < 1 wk duration;
Febrile illness (temperature > 38.3C) for > 48 hrs;
Neurologic signs or nuchal rigidity, etc.;
No immediately identifiable specific cause.
 3. Syndromes caused by cholera, plague, yellow fever, malaria or tuberculosis, and any serious endemic disease caused by antibiotic-resistant bacterial or protozoan pathogens (resistance to be monitored routinely);
 4. Similar syndromes in animals (unexpected clusters of deaths accompanied by severe respiratory or CNS signs, or caused by antibiotic-resistant bacterial or protozoan pathogens).

Rationale for the Syndromes To Be Monitored

- a. There are compelling reasons to focus initially on the particular conditions listed above:
 - a) The known pathogens causing these syndromes include some of those that are among the *most transmissible* and hardest to control, with high potential for rapid spread;
 - b. The syndromes are among the most distinctive and *easily recognized* clinically, and the most likely agents causing these syndromes in the past are known and can be tested for;
 - c. They are among the most important diseases, often with high fatality rates, including some of those with the greatest history of emergence or *potential to emerge*;
 - d. The target syndromes are *not subject to systematic surveillance at present*; the program would complement as well as extend existing efforts, including those already planned or underway in various programs at WHO, and could tap their expertise in tracking related or overlapping diseases;
 - e. The syndromes are *controllable*, in many cases, if recognized early; and
 - f. The appearance of antibiotic resistance needs to be recognized early so that new antibiotics can be developed before resistance becomes widespread.

Changes in prevalence or distribution of the known agents causing the suggested syndromes would be significant, and it would be very important to recognize early any new or previously unknown agents, or the appearance of antibiotic resistance in any bacterial agents encountered. A number of the most recent emerging infections would fit under these criteria.

In choosing an initial focus for a program of this kind, several criteria must be considered. In the field, especially in areas with only limited laboratory capabilities, recognition of an emerging human infection is most likely to begin with a cluster of unexpected and unexplained deaths, accompanied by signs suggesting an infectious etiology (e.g. fever and severe respiratory involvement, or fever and severe neurological manifestations). Syndrome surveillance is, therefore, the natural starting point. The draft 1996-1997 plan for the new

WHO Division of Emerging and Other Communicable Diseases Surveillance and Control points out that successful surveillance systems have already been carried out in some developing countries for a limited number of target syndromes.

The syndromes chosen for initial inclusion in the program should be few, easily identified clinically and, in order to justify the laboratory diagnostic effort, should have a reasonably high likelihood of being significant. The syndromes suggested here meet these criteria. Other important candidates, such as hemorrhagic fevers and systematic surveillance of foodborne diseases, have been omitted intentionally from this proposal in order to limit the initial requirements and avoid duplication of programs at WHO.

Respiratory infections are high on the list of potential threats (consider pandemic influenza, for example). Pneumonia and influenza are among the leading causes of death even in high income countries. Respiratory infections are often highly transmissible (excluding some obvious exceptions, such as pneumococcal pneumonia in the debilitated elderly), and are among the hardest to control; thus they have great potential for rapid spread. They also include some of the most feared diseases, as recently demonstrated by the events that followed the reports of pneumonic plague in India.

The history and lethality of such respiratory infections as pandemic influenza and pneumonic plague, and the potential for rapid spread of infections transmitted by the respiratory route, led the distinguished expert Cedric Mims to suggest that these infections represent the greatest danger and require special scrutiny. On the other hand, although respiratory infections are common, acute respiratory infections are rarely very severe and, therefore, one that strikes with great severity is both noticeable and potentially of great public health significance. Most of the most recent emerging disease incidents, including the outbreaks of hantavirus pulmonary syndrome in North America and elsewhere, the outbreak of plague with pneumonic transmission in India, and the incident caused by a new morbillivirus in Australia, with fatalities in both humans and horses, were pulmonary.

Encephalitis/meningitis, similarly, includes some infections with a history of rapid epidemic spread (e.g. *Neisseria meningitidis* [meningococcus]), and many that are significant regional threats, such as the meningococcus in parts of Africa and Asia, Japanese encephalitis in Asia, and a number of encephalitides in the Americas, including, among others, Eastern and Venezuelan equine encephalomyelitis. These conditions often strike the young and may have significant sequelae, reducing future productivity. Many are controllable if recognized, so that there is immediate value in the surveillance activity. Serious encephalitis/meningitis is relatively infrequent as a disease entity, but when it does occur, case fatality rates are often high; even in high income countries, meningitis mortality averages about 30% overall and 50% for patients hospitalized specifically with meningococcal meningitis.

The moderately low overall incidence of the relatively severe manifestations specified in the

case definitions for surveillance means that the Centers would not be swamped with insignificant cases but, on the other hand, would likely encounter enough potential cases, most caused by already known and readily identifiable agents, to keep the system working effectively. If it should develop that there are too many cases to monitor effectively, the case definitions could be further limited. Some agents of these diseases, such as *Streptococcus pneumoniae* (pneumococcus), are important cosmopolitan pathogens, for which detection and identification methods are well-established and within the capabilities of an average clinical microbiology laboratory in an industrialized country. Some of these bacteria might develop drug resistance or suddenly manifest invasiveness, and it would be important to recognize such changes as early as possible to allow effective action. There may well also be some cases of the specified syndromes caused by major bacterial pathogens already known to have acquired invasive manifestations, and these would benefit from further investigation by the Centers.

These disease presentations, because of their severity and distinctiveness, have a reasonable likelihood of coming to the attention of health care workers and are relatively easy to recognize. For these reasons it should be possible to train local assistants to recognize these conditions in the field and to enlist local help in epidemiologic investigation.

Despite the importance of unexplained ARDS and encephalitis/meningitis, there is at present no systematic surveillance for these conditions. For example, there are no regularly functioning field systems for identifying meningitis in areas of high endemicity, although there are some occasional efforts and a few reference laboratories specifically for meningococcal meningitis. **The program would therefore provide a test track for developing and applying new surveillance strategies;** it would effectively complement and greatly enhance present surveillance capabilities, including those now being strengthened at WHO. On the other hand, there are existing laboratory-based networks with experience in tracking influenza and polio; their expertise, both in scientific matters and in overcoming practical problems, could be solicited during establishment of the program.

Along with surveillance for the two defined syndromes, the Centers should be able to identify the common diseases with high fatality and high epidemic potential: cholera, plague, yellow fever, tuberculosis, and malaria. The pneumonic form of plague, and cerebral malaria, are included under the syndromes suggested for targeting. Few laboratories now have the capability to diagnose plague or yellow fever, and referral of specimens to distant reference laboratories takes too long. The procedures for identifying all these pathogens are operationally similar to those used for the likely pathogens causing the targeted syndromes. Centers should generally be able to identify any other serious diseases endemic to their regions (for example, in West Africa these would include Ebola, Lassa and Marburg), both as a regional benefit and to eliminate any possible confusion with targeted syndromes. Thus, each Center would support a "basket" of basic microbiology capabilities (essentially as represented in J. Vandepitte, K. Engbaek, P. Piot, and C.C. Heuck, "Basic laboratory procedures in clinical bacteriology," Geneva: World Health Organization, 1991). Any bacterial pathogens identified should be

routinely tested for major antibiotic sensitivities to provide early warning of emerging resistances. Data obtained would be provided to programs already in progress, such as WHONET. The overall feasibility of this approach has been demonstrated by IBIS, the Invasive Bacterial Infections Surveillance program in India (part of INCLEN, the International Clinical Epidemiology Network).

3. PROGRAM OPERATIONS AT NETWORK CENTERS

Program Activities at Each Center:

- a. Case finding, clinical screening, investigation and diagnosis of all cases in the area with the targeted syndromes;
- b. Reporting to the program office of all findings on the targeted syndromes and other serious or unusual diseases (whether diagnosed or not) without delay, with requests for help in diagnosis, treatment or containment, if needed;
- c. Development and maintenance of a local/regional network to report suspected cases, collect specimens, refer patients for further testing, assist the Center in subsequent field investigations, and alert neighboring areas;
- d. Laboratory testing of clinical specimens for a standard set of pathogens including the likely agents for the targeted syndromes and for cholera, plague, yellow fever, tuberculosis, malaria, or any other serious, locally endemic disease (high fatality, high epidemic potential);
- e. Cataloging and permanent storage of all sera and other samples;
- f. Referral of notable, unusual or undiagnosed specimens, regardless of syndrome, to designated reference laboratories;
- g. Epidemiological field investigation and field ecology studies, when warranted (with assistance mobilized by the program office if necessary), and collaboration, when possible, with ongoing ecological studies such as the UN's Man in Biosphere Program (MAB), to follow up important or unusual findings in order to identify the causes of disease and future means of prevention;
- h. Receiving and examining reports from the central office, other Network Centers and other sources and alerting the local clinical network if a threat is perceived;
- i. Providing their regional networks with incentives for cooperation in the form of training, regular meetings and seminars, diagnostic and other information, advance warning of possible outbreaks, and help in obtaining emergency assistance;
- j. Close liaison, capability- and information-sharing with national and regional medical and veterinary schools, Ministries of Health, Agriculture, Forestry, Fisheries, Hydrology, and other national and regional governmental and non-governmental organizations with medical and related interests.

Network Centers must be able to identify the important cosmopolitan pathogens that are frequent causes of the suggested target conditions, including, for humans, influenza,

adenoviruses, *Yersinia pestis*, *Streptococcus pneumoniae*, Group A *Streptococcus*, and *Plasmodium falciparum* (cerebral manifestations), as well as the known hantaviruses.

Detection and identification methods for these organisms are well established. The program office would assure that each Center has a microbiology laboratory meeting these standards, and capable also of performing antibiotic sensitivity testing routinely on any bacterial isolate. Simplified technology is now available for this testing, and WHONET 3 software can be used to standardize reporting.

Standard operating procedures, including case definitions, clinical diagnosis and treatment procedures, types of diagnostic samples to be taken and standard procedures for doing so, would be provided by the program office. Training, diagnostic reagents, and any other materials and small equipment that might be lacking to bring each Center up to the program requirements would also be provided. Centers with particular types of expertise would participate in the training and provision of aid to other Centers. The Centers, in turn, would similarly assist their regional networks to perform their program functions. Funding for additional personnel, capital equipment or infrastructure needed to carry out the program would have to be obtained by each Center bilaterally with the help of the program office.

4. OPERATIONS AT THE PROGRAM OFFICE

The Program Office, headed by a program director, would be responsible for the initial organization and subsequent coordination of the network and the provision of support for critical functions to the Network Centers. In carrying out its work the office would consult with an Advisory Committee of outside experts, many of whom could be drawn from the ProMED Steering Committee or Working Groups on , Animal and Plant diseases, as well as from the Network Centers.

Initial Operations at the Program Office:

- a. Organization of a small network of Centers in the developing world, strategically located and possessing most or many of the capabilities needed for operation of the program;
- b. Initial specification of case definitions, specimens to be taken, standard clinical and laboratory diagnostic procedures, and guidelines for treatment and epidemiological followup for the diseases of interest (a manual containing these specifications would be reviewed and improved periodically, in the light of the Centers' experience and of new information);
- c. Provision of initial training and of diagnostic reagents, other materials and critical equipment that might be required to bring each Center up to the program requirements.
[Note: existing WHO programs could provide considerable aid in carrying out

operations c), d), e) and f)];

- d. Designation of a system of reference laboratories for the diseases of interest; and provision of arrangements for transport and storage of samples;
- e. Identification of resources that could be called upon for training or aid in epidemiological and other field investigations, when needed;
- f. Identification of resources for emergency aid in responding to outbreaks to prevent their spread, and development of procedures for its rapid mobilization (in collaboration with appropriate WHO programs); and assistance to the Centers in developing response plans. *Aid should be channeled through the program, and local personnel should be in charge;*
- g. Establishment of an electronic communications system and fax backup linking Centers to the program office and the office to other sources of surveillance information and to interested groups, including national health authorities, international organizations, research bodies, etc. (this would include provision of necessary communications equipment and training at the Centers);
- h. Development of standard reporting formats, merged or harmonized with existing reporting systems such as those of the Office International des Epizooties (OIE), WHONET, etc;

Continuing Operations at the Program Office:

- \. Operation of the network communications system; compilation, analysis, and dissemination of outbreak and other data received from the Centers and other sources, together with relevant information and recommendations. Also, when possible, arrangement for telemedical consultations to bring specialized expertise to each site when needed;
- a. Maintenance of close liaison and data sharing with international organizations, including various WHO programs, OIE, FAO (the UN Food and Agriculture Organization), the International Office of Migrations, the Office of the High Commissioner for Refugees, the Red Cross, UNICEF, UNDP, UNIDO and the World Bank; government agencies such as National Institutes of Health, the U.S. Centers for Disease Control (CDC), and similar agencies in other countries; and non-governmental organizations such as Medecins Sans Frontieres;
- b. Liaison and data sharing with UNEP and other international, governmental and NGO environment-monitoring agencies, including NASA (The U.S. National Aerospace Administration, which collects data on weather and climate change by remote sensing, from which data on vector distribution is derived and integrated into geographical information systems). Working with these organizations, it might be possible to issue advance regional alerts based on predictions of possible outbreaks;
- c. Maintenance of contacts with ProMED-mail, an electronic reporting system open to both confirmed and unconfirmed reports of disease outbreaks of all kinds from any source. This system permits free discussion, elicits new ideas and disseminates

- information that might not be widely available otherwise;
- d. Periodic certification of Network Centers' capabilities to carry out the necessary activities, and consultation on possible improvements that could be made (this would involve visits and provision of positive and negative control samples for diagnostic quality assessment);
 - e. Procurement and provision of diagnostic reagents, where needed (some could be arranged through existing WHO programs);
 - f. Local capability building, with initial emphasis on diagnostic self-sufficiency, through activities organized and financed by the program office or arranged in cooperation with other programs. These activities would include:
 - o Regional training courses, conferences and workshops,
 - o Provision of specialized equipment,
 - o Exchange of personnel among Centers,
 - o Yearly or more frequent meetings of personnel from the Network Centers for discussion among themselves and with invited experts for resolution of problems, introduction of new technology, etc.,
 - o Rapid provision of new information.
 - g. Development of, or contribution to, a comprehensive infectious disease database, accessible to all, including molecular epidemiology and geographic distribution of pathogens and vectors, interfaced with available ecological and meteorological data. This database would incorporate existing databases from other sources and those already under development (such as the virus database in preparation by the International Committee on Taxonomy of Viruses, and the veterinary database being developed by OIE with FAO and WHO);
 - h. Preparation and public issuance of guidelines for recognition, prevention and control of specific diseases whenever the network's experience would be of general value;
 - i. Issuance of "infectious disease assessments" of proposed large-scale projects affecting the environment, and of large-scale events affecting populations, with the help of the appropriately-located Centers;
 - j. Promotion of global awareness of the importance of emerging infectious disease surveillance and control and;
 - k. Nomination of candidates for addition to the Network as new Centers or as possible future Centers, for preliminary cooperation.

Local capability building would be an essential function of the program in order to ensure sustainability of the system, relevance to local needs, and local government support for the program. Personal contacts and exchanges among network members should be a central feature. The OIE, for example, considers that the contacts developed at their annual and regional meetings are the most important factor underlying effective reporting. In its training activities the program office should, whenever possible, call upon Centers with the required expertise to assist in training personnel in other regions.

In order to provide practical diagnostic reagents, procedures and other protocols that can be effectively used and consistently applied in the field, the program office would consult regularly with personnel from the Centers as well as with expert advisors as it develops and periodically revises the manual of standard operating procedures. The office would provide cooperating institutions and programs with surveillance information from the Centers to encourage and help direct the development of improvements in applicable technology and forecasting.

The program's communications network would seek to link with any existing related systems, so that the information compiled from the Centers would become part of a widely accessible and broadly based global infectious disease reporting system.

5. FINANCING OF OPERATIONS

Assurance of reliable funding by donors for startup and for an adequate period of time to test the program will be required before the program can get underway. Dedicated funds will be needed to support the program's office staff and operations, which may include the provision of training, materials, and certain equipment to the Centers. When appropriate, the program office would contract for certain functions to be carried out by WHO programs or other organizations (such as SatelLife), thereby avoiding duplication of effort and keeping the size of the program office to a minimum. Financial contributions by donors directly to individual Network Centers for items such as special programs, buildings, infrastructure, capital equipment and salaries would be solicited by the program office when needs have been identified. Donors should make clear to participating nations that cooperation with the program and continued maintenance of the Centers would be taken into account when considering future aid *in any field*.

6. EVALUATION AND FUTURE EXPANSION OF THE PROGRAM

This program, linked with other global, regional, and national surveillance programs that are being or may be developed, would constitute the first stage of progress toward a global capability for monitoring emerging infectious diseases. The program would be able to test possible directions for future development.

Evaluation of the program would be needed for improving and strengthening it and for deciding on possible future expansion. Procedures for evaluation should be developed in consultation with the Centers. There are, of course, no standard criteria for assessing overall success in identifying and preventing the spread of emerging infections; appropriate criteria will have to be developed and tested. However, a number of the activities could be assessed in terms of their success in meeting operational goals, such as the degree of participation in, and the results of, the laboratory quality assessment program; the level of personnel competence

and enthusiasm; success in the adoption of new capabilities; success in casefinding and follow-up; effectiveness of surveillance for endemic diseases to which conventional assessments can be applied; amount, timeliness, relevance, and quality of information contributed; and cost-effectiveness of activities.

Fundamental principles of future expansion should be, first, *to make full and effective use of existing resources*, and then *to add to them incrementally wherever the need is greatest*. If the first stage is successful, the program could expand initially in either of two ways: by broadening the activities at existing Centers or by adding additional Centers to the network.

Probably the most urgent and readily adopted expansion would be the inclusion of additional syndromes for surveillance. If the program is successful, the ultimate goal will be to investigate all unexplained and unexpected deaths. In the long run, the inclusion of more intensive agent-based as well as syndrome-based surveillance might be desirable. This would entail greater emphasis on vector and other field ecology studies. It will also be desirable to expand training and resources to enhance community involvement and strengthen the local clinical and referral networks that back up the Centers.

New Centers with the necessary capabilities, located in regions where coverage is needed, could readily be added to the network. As a start, the collaboration of such facilities in monitoring and reporting the specified syndromes should be welcomed. However, in most cases, capabilities will be inadequate and will need upgrading. As a first step, promising facilities could be identified and each could be paired with a member Center that would act as a consultant and would provide diagnostic materials, training through courses and exchange of personnel, etc. Aid for capital upgrading would be solicited; if a facility made stable progress, it would be accredited as a Network Center.

As new Centers are added, linkage or integration of animal and human diagnostic laboratories, vector and environmental field studies, and other surveillance components should be a major consideration. In addition to interdisciplinary stimulation, dual use of some facilities and personnel would be efficient and would extend capabilities at minimal cost.

Ultimately, there may be critical locations in which no suitable facilities exist at all. The program could point out the need and encourage the development of appropriate institutions in these locations, to serve as regional facilities as well as Network Centers.

Global resources for emergency response to unexpected infectious disease outbreaks are very limited at present. The proposed program would improve interim planning and effective use of existing resources, but ultimately, regional emergency response capabilities must be developed. Development of some of the Network Centers as sources of the trained personnel, equipment and supplies needed for global emergency response would be a long-term goal of the proposed program.

The program's experience would provide information on regional infectious disease risks and capabilities for monitoring and control. On this basis, the program would be able to make recommendations for strengthening local and national programs and for the development of some of the Centers, in strategic locations, as international health research centers with epidemiological, socio-behavioral, laboratory and clinical expertise and with the capability for applied research directed to the solution of infectious disease and other health problems. Most developing countries do not have the means to provide the critical mass of research and supporting staff, institutional infrastructure, funds, and international access that is required. In addition to disease surveillance, international health research centers - similar to the International Center for Diarrheal Disease Research in Bangladesh - could develop new and improved tools for diagnosis, prevention and management of selected diseases; facilitate their application; develop health research manpower for national institutions, to build their capacity; and provide emergency response to contain regional outbreaks of disease.

Desirable Criteria for Network Centers

Network Centers (which may include groups of several collaborating institutions in the same area) should have:

1. Access to potentially significant (including novel) clinical observations from the field and access to the patients;
2. A local laboratory-based diagnostic system capable of differentiating common and endemic illnesses from the syndromes of interest, and of recognizing the usual agents causing those syndromes;
3. Capability for epidemiologic investigation;
4. Capabilities in pathology and in field ecology (e.g. zoology, entomology and behavioral science; and
5. Linkage with national public health authorities, medical schools, animal health facilities and other health-related institutions in the region.

Possible Organizational Framework for a Program To Monitor Emerging Diseases

The program would comprise the Network Centers, the program office (as part of an executing agency), a Board of Directors with an Executive Committee, an Expert Advisory Committee, and a fiscal agent . It could be co-sponsored by a group of agencies such as the World Bank, WHO, OIE, FAO, UNDP, The Rockefeller Foundation, etc., similar to the Consultative Group for International Agricultural Research (CGIAR).

The Network Centers

The nature of the Network Centers, and their activities under the program, are discussed in the main text of the proposal. Centers would be selected by the Board of Directors, in consultation with the Expert Advisory Committee, from among nominations presented by: co-sponsors of the program, regional health organizations, National Ministries of Health, and the program office (subsequent to the initial selections). Nominators would be asked to propose candidate Centers that approximate the Criteria, with particular emphasis on clinical access. Initially, it would be desirable for at least one of the Centers to include access to animal diseases.

A Network Committee composed of the Directors of the Centers would meet periodically with the Program Director to discuss the efficacy of the program and ways in which it could be improved.

The Executing Agency and the Program Office

The program would be established under an executing agency. The program office could be located in or near the headquarters of the executing agency, or at one of the Network Centers. The Program Director would appoint the staff. In addition to the functions discussed elsewhere, the office could also supply secretariat services for the Board, Executive committee and Expert Advisory Committee, if they so wished.

Funds for the program would be under the control of the program office, which could contract for certain functions to be carried out by existing programs of other organizations, thereby avoiding duplication of effort and keeping the size of the program office to a minimum.

The Board of Directors

Governance and ultimate authority would be vested in the Board, composed of the co-sponsors; additional donors, including government agencies; and governments or other organizations that provide substantial support for individual Network Centers. To keep the size of the Board from becoming unwieldy, a maximum size could be set and maintained by electing or rotating members other than the co-sponsors, or setting a minimum contribution for membership. Key international agencies and relevant non-profit organizations and foundations in a position to provide technical support to the program, such as CGIAR, its member center, ILRAD (the International Laboratory for Research on Animal Diseases), the American Council on Arthropod-Borne Viruses (actually an international organization that does some surveillance), ORSTOM, INCLIN, FETP, and SatelliLife (a non-profit organization that provides electronic communications to health workers in developing countries and remote areas), as well as non-donor governments that host Centers, could be invited to participate from time to time at Board

meetings.

The Board would elect a small subgroup to serve as a standing Executive Committee to oversee program operations between Board meetings.

The Board would set the overall strategy for the program and monitor its performance; approve the budget and assure the program's cost effectiveness; appoint the Expert Advisory Committee and, in consultation with that Committee, appoint the Program Director, and approve nominations for Center membership in the network.

Program activities such as those outlined in this proposal would ultimately have to be ratified or modified by the Board of Directors, with advice from the Program Director and the Expert Advisory Committee.

The Expert Advisory Committee

The Expert Advisory Committee would be composed of about 15 top outside experts in the fields relevant to the program, from all parts of the world. Initially, many of the experts could be drawn from the ProMED Steering Committee. They would maintain the scientific quality of the program by providing independent input to the Program Director on scientific and technical questions (including those specifically related to the syndromes under surveillance), and would assist in evaluating and recruiting Centers. The Committee would work with the Program Director in planning and executing the functions of the program and drawing up its budget, and would periodically evaluate the effectiveness of the program and suggest improvements.

The Fiscal Agent

One of the co-sponsors would act as the fiscal agent for the program and would establish a trust fund for contributions to the program. Funds for the program would be dedicated for that purpose only. The fiscal agent and other donors should make clear to participating nations that cooperation with this program and continued maintenance of the Centers would be taken into account when considering future aid.

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