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Challenges to Global Surveillance and Response to Infectious Disease Outbreaks of International Importance

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This article presents a notional scheme of global surveillance and response to infectious disease outbreaks and reviews 14 international surveillance and response programs. In combination, the scheme and the programs illustrate how, in an ideal world and in the real world, infectious disease outbreaks of public health significance could be detected and contained. Notable practices and achievements of the programs are cited; these may be useful when instituting new programs or redesigning existing ones. Insufficiencies are identified in four critical areas: health infrastructure; scientific methods and concepts of operation; essential human, technical, and financial resources; and international policies. These insufficiencies challenge global surveillance of and response to infectious disease outbreaks of international importance. This article is intended to help policymakers appreciate the complexity of the problem and assess the impact and cost-effectiveness of proposed solutions. An assessment of the potential contribution of appropriate diagnostic tests to surveillance and response is included.

The emergence of new infectious diseases and the resurgence of diseases previously controlled by vaccination and treatment are creating unprecedented public health challenges. Recent disease outbreaks of Sudden Acute Respiratory Syndrome (SARS), multidrug-resistant tuberculosis, Ebola viral hemorrhagic fever, West Nile viral encephalitis, intentional anthrax, and H5N1 viral infections in humans have heightened concerns about global health security and global economic stability.[1–4]

In response to these concerns, government and global health leaders worked together to revise the International Health Regulations in May 2005 (IHR 2005).[5,6] The IHR 2005 provides both the legal framework and the requirements for all countries to be able to detect and contain infectious disease outbreaks. As of June 2007, all countries are required to develop and maintain surveillance, reporting, verification, and response mechanisms at local, intermediate, and national levels. Any country with knowledge of a disease outbreak of international concern must report it to the World Health Organization (WHO) within 24 hours, regardless of where the emergency is located.[7–9] These important policy changes are necessary for timely recognition and effective containment of disease outbreaks of international public health significance; however, they may not be sufficient, and concerns about global capacity persist.

Major Components of Global Surveillance and Response Programs

Rapid and effective response to a confirmed infectious disease outbreak is a complex, multistep process. It conven-

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tionally begins in surveillance systems with the recognition and reporting of an unusual disease outbreak. Reports of outbreaks that appear to be credible and that may have international public health significance must be verified by the affected country; response to the outbreak includes the initial confirmatory investigation as well as outbreak containment. In this report, the basic components of surveillance and response programs are defined as:

- ***Surveillance:*** systematic monitoring for a case (or cases) of an unusual disease and/or an unusual cluster of diseases—the stimuli for the initial disease outbreak report;
- ***Reporting:*** an account of the initial disease outbreak; the report reflects an assessment of credibility and of potential public health significance;
- ***Verification:*** inquiry to affected country and the initial investigation to verify the disease outbreak; and
- ***Response:*** intervention and containment of the disease outbreak.

The term *infectious disease surveillance* is used in public health and policymaking communities to convey a variety of concepts, methodologies, and actions.[10–13] Some infectious disease surveillance programs monitor a disease over time (e.g., the WHO's Global Influenza Surveillance Network),[14] while others attempt to detect and track specific diseases (e.g., the U.S. Department of Defense Biological Threat Reduction Program).[15] Still others report on unusual clinical cases or disease clusters that are judged by experts to be of concern to the infectious disease community.[16] Some systems rely on case definitions* and clinical observations; others monitor laboratory test results (e.g., serology); some use analysis of samples routinely collected by sentinel clinicians; some derive data from routine computer-based searches of patient or public health records; and some use media reports of disease outbreaks.†

Notional Scheme of International Surveillance and Response

This notional scheme of international surveillance and response is based on published literature (Figure 1).[24,26] It begins with a sick person who may be suffering from an unusual disease, or with a group of people who comprise an unusual cluster of cases; it ends with disease outbreak containment. Surveillance, reporting, verification, and response are the essential functions of the scheme; these are illustrated by the programs (Figure 2).

In practice, the flow of information and action within the scheme are often disrupted. For example, by regulation, a clinical case of smallpox must be reported to WHO immediately;[6] however, an "apparent smallpox" outbreak in the Sudan was discovered and reported to WHO in October 2005 by a Global Outbreak Alert and Response Network (GOARN) partner, Médecins Sans Frontières. The disease was identified as monkeypox, the first case of which had occurred 5 weeks previously. Subsequently, the Médecins Sans Frontières team found small clusters of self-limiting monkeypox cases within the community.[27,28] Had the outbreak been smallpox, a disease that is easily transmitted and more severe than monkeypox, arguably the 5-week delay could have resulted in many more cases and caused an international public health emergency.

Similarly, the first SARS cases occurred in November 2002, but they were not recognized as such, nor were they reported to WHO, for several months.[2] Triggered by a ProMED-mail report in February 2003,[29] WHO was officially notified of a "subsequent" SARS outbreak involving 305 cases, including 5 fatal ones. One month passed (March 2003) before the affected country requested assistance from WHO; by then SARS had spread to another country.[26] Fortunately, people with SARS are not highly contagious until they are very ill, so the transmission rate is low. Although the impact on international public health was limited by effective outbreak containment measures, the impact on international trade and travel was estimated to be $18 billion.[30]

Program Summaries

The program summaries that follow illustrate the four components of infectious disease containment efforts: surveillance, reporting, verification, and response. These particular programs were chosen because: (1) they represent some of the more ambitious international infectious disease surveillance and response efforts; (2) they focus on human infectious diseases with the potential for international public health impact; (3) they are associated with outbreak containment efforts; and (4) they collect information on a daily or weekly basis. Notable practices and achievements were identified; these are summarized in the subsequent section.

Program summaries are based on open-source literature and interviews with one or more program staff. The program summaries begin on page 210.

*Case definition is a group of signs and symptoms that characterize, but may not exclusively belong to, a disease.

†More recently, surveillance systems are being used to monitor surrogate markers of disease, such as sales of over-the-counter healthcare products, school absenteeism, and calls to poison information centers. These types of surveillance systems were not included in this study.[13,17–21]

Figure 1. Notional Scheme of Global Surveillance and Response

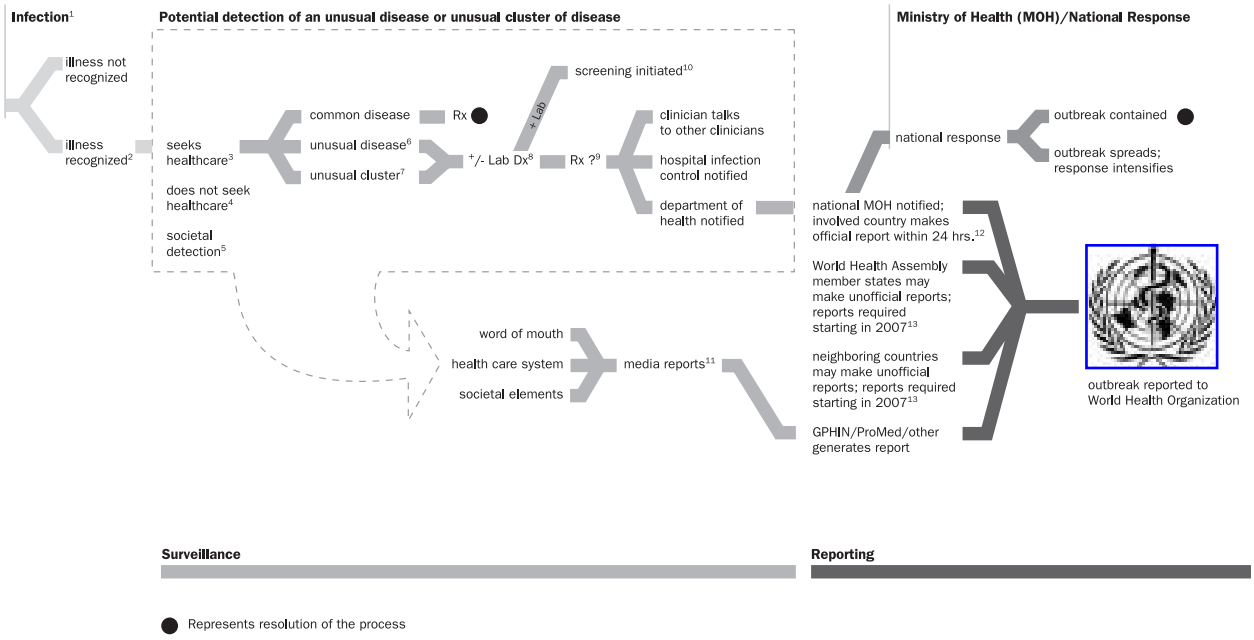
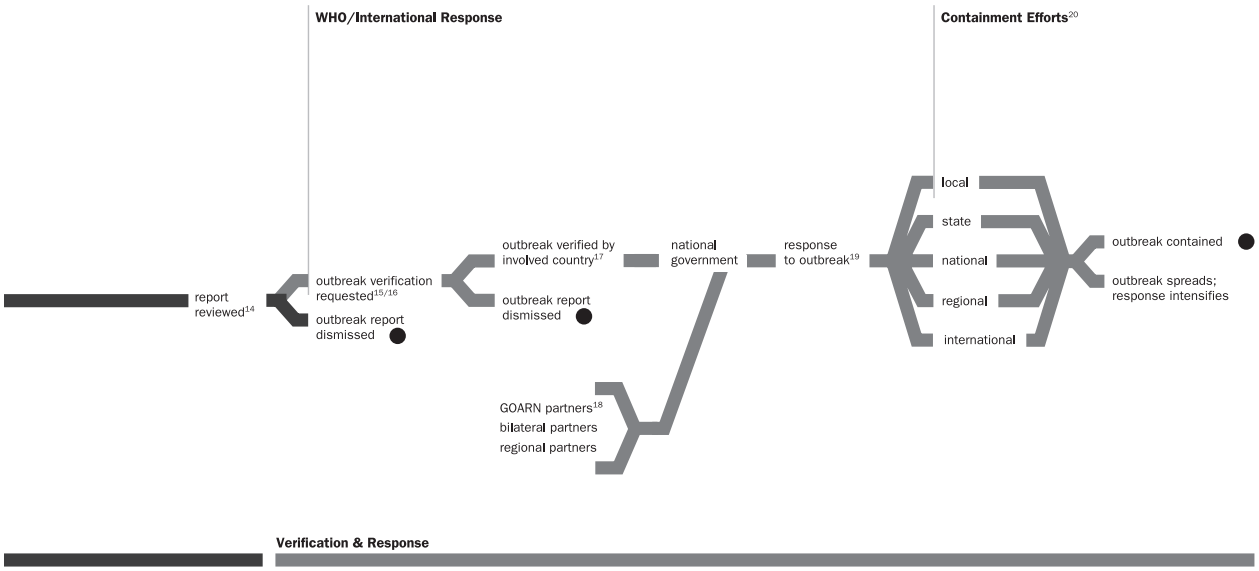


Figure 1. Some of the factors that affect the flow of information in the scheme are detailed in the footnotes to the figure.[22]

1. Once infected, onset of illness may be fast or slow. Self-recognition of illness depends on the severity of signs and symptoms; these can range from unnoticeable to mild, moderate, or severe.
2. If a person recognizes he or she is sick, he or she may or may not seek health care.
3. If a sick person seeks health care, the healthcare provider may diagnose a common or an unusual disease.
4. Some reasons for not seeking care include: health care is unavailable; health care is unaffordable; the healthcare system is not trusted; illness may be very mild; the disease is stigmatized; severe illness prevents healthcare seeking.
5. A disease outbreak may be detected by other societal elements, such as schools (increases in absenteeism), first responders (increases in emergency rescues), or pharmacies/traditional healers (increases in medicine sales).
6. If an unusual case of disease is recognized, particularly if it meets the case definition (e.g., watery diarrhea) for diseases of concern (cholera), one or more notification processes *may* begin. The healthcare provider may informally discuss the case with other clinicians; hospital infection control may be notified; the ministry of health may be notified.
7. An unusual cluster of disease cases is an outbreak of a "common disease or syndrome" that is unusual with respect to season, location, demographics, or morbidity/mortality. For example, based on historical analyses of influenza pandemics, abnormal clusters of disease may be the first warning of the emergence of a strain with pandemic potential. Possible signals include an early or an extended flu season, severe illness in younger people, increased mortality, or changes in mortality patterns (i.e., seasonal or demographics of fatal cases). Recognition of such trends is difficult without making comparisons with historical population-based data.
8. If available, a diagnostic test may be ordered. To be useful in the primary or emergency care facility, such diagnostic tests must be simple and affordable without sacrificing accuracy. When performed on patients who have signs and symptoms of disease, the results of the test must provide actionable information for care of the patient, for infection control in the healthcare facility, for outbreak reporting, for investigation, and for rapid containment.
9. The diagnostic test results may reveal an unusual disease. If the patient was not hospitalized, it may be difficult to relocate him and provide appropriate treatment and/or vaccination.
10. If the laboratory test confirms the sick person has a disease that is vaccine preventable (e.g., polio), screening for asymptomatic carriers and vaccination campaigns may be initiated.
11. The news media may report disease outbreaks from a variety of information sources, including societal sources, healthcare providers, or other people who work in hospitals, health departments, or other government departments.
12. Concerns about the impact of the disease outbreak on international trade and travel responses may dissuade countries from reporting the disease outbreak or requesting assistance. Such delays affect the size of the outbreak in the country as well as regional or international spread of the disease.[23]



Graphic by Megan Van Wagoner

Figure 1. *Continued.*

13. Member States of the World Health Assembly that have agreed to IHR 2005 are responsible for reporting outbreaks of seven diseases, as well as any unusual disease outbreaks and unusual clusters of disease cases with potential for international public health impact, to the World Health Organization within 24 hours, regardless of the location of the outbreak.

14. WHO staff reviews disease outbreak reports daily; several questions are considered before WHO takes action on the report:
    - Is the disease one of seven that is reportable (smallpox, plague, yellow fever, cholera, polio, SARS, or influenza caused by a new strain of human virus)?
    - Is it an unknown disease?
    - Is there potential for spread beyond national borders?
    - Is there a serious health impact or unexpectedly high rates of illness or death?
    - Is there potential for interference with international trade or travel?
    - Does the country have the capacity to contain the outbreak?
    - Is the outbreak suspected of being caused by a laboratory accident, or a deliberate act?[6]

15. If the report seems credible and the outbreak could potentially be a threat of international public health significance, a request for verification is relayed to the appropriate WHO regional office and the involved country is asked to investigate the outbreak report.[6]

16. WHO offers assistance to the country for the investigation of the reported disease outbreak. Assistance includes, but is not limited to, information, diagnostic tests, and field staff. In most cases, the involved country must request the assistance. The type and amount of assistance reflect the disease, the size of the outbreak, and the national resources of involved countries.[24]

17. If the outbreak is verified, WHO will provide additional resources, such as therapeutics and vaccines; maintain situational awareness; and coordinate any and all aspects of the response, including the involvement of WHO's Global Outbreak Alert and Response Network (GOARN).[24]

18. GOARN is a voluntary technical partnership of approximately 140 institutions coordinated by WHO to support countries in disease outbreak response, primarily through the deployment of multidisciplinary teams of experts.[25]

19. The response to the outbreak will occur on multiple levels within the involved country. If the outbreak has spread beyond the borders of the involved country, responses of countries in the region and/or the international community may occur simultaneously.

20. All funds required for international response to disease outbreaks are donated at the discretion of World Health Assembly Member States.

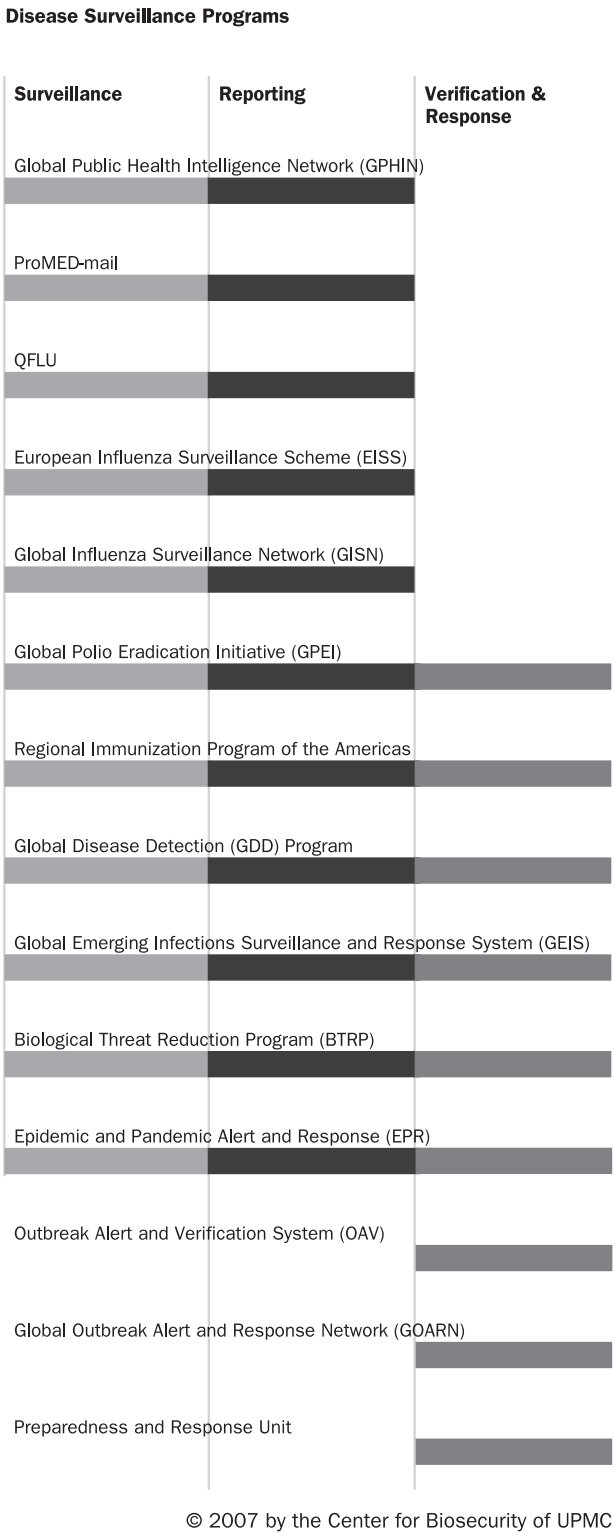


Figure 2. The components of the scheme (surveillance, reporting, verification, and response) play essential roles in infectious disease outbreak containment; these are illustrated by the programs.

Global Public Health Intelligence Network (GPHIN)

www.phac-aspc.gc.ca/media/nr-rp/2004/2004_gphin-rmispbk_e.html

Purpose: Global Public Health Intelligence Network (GPHIN) provides reports of disease outbreaks primarily derived from news media sources to WHO, government and public health leaders, and subscribers interested in global health.

History and operational characteristics: GPHIN was created in 1998 by Health Canada's Laboratory Centre for Disease Control in collaboration with WHO. It is a fee-based electronic reporting service that searches electronic global media sources for reports of public health importance and provides them to its subscribers. (Subscription fees vary depending on the type and size of the organization requesting the service. Free trial periods of 30 to 90 days are occasionally permitted.)

Each day, GPHIN scans thousands of electronic media reports from news source providers such as Factiva (www.factiva.com) and Al Bawaba (http://www.albawaba.com/). Factiva provides coverage of news reports in English, French, Russian, Simplified and Traditional Chinese, and Spanish; Arabic news reports are obtained from Al Bawaba. Farsi news reports are manually entered into the system by the GPHIN analyst responsible for Farsi content. GPHIN also receives official disease outbreak reports from ministries of health.

GPHIN uses an automated system to make a first determination of priority, with final determination made by a team of analysts. Approximately 7–10 alerts are emailed or posted to the GPHIN website daily, the majority of which focus on infectious diseases in humans and animals. Alerts of other significant events involving chemical and radioactive exposure, food safety and security, product safety, and natural disasters also are emailed. Alerts may include commentary on: estimation of an incident's magnitude, geographic distribution of the incident, control and prevention measures that have been implemented (and/or considered), concerns of the general public, and political implications.

Most GPHIN subscribers are from government organizations and other organizations interested in public health, but others come from nongovernmental organizations, business, the military, and other organizations such the North American Treaty Organization (NATO). WHO also has access to the GPHIN web postings and alerts; GPHIN news reports comprise approximately 40% of WHO verified disease outbreaks.[31] GPHIN has recently begun a collaborative effort with the U.S. Centers for Disease Control and Prevention (CDC) to create a program for information sharing and event verification.

Regions/countries served: Worldwide; articles currently reviewed in seven languages: Arabic, English, French, Russian, Simplified and Traditional Chinese, and Spanish.
Funding/budget/staff: Annual budget (including operational costs and system development) is approximately $3.5 million Canadian. All subscription fees are used solely for system development. The bulk of GPHIN funding comes from the Canadian government. GPHIN operates with seven multilingual analysts.

ProMED-mail

www.promedmail.org
Purpose: ProMED-mail is an internet-based surveillance system that disseminates information on outbreaks of infectious diseases and acute exposures to toxins based on media reports and reports from subscribers. It reports on diseases that affect human health, including those in animals and in plants grown for food or animal feed.[32]
History and operational characteristics: The Program for Monitoring Emerging Diseases (ProMED)-mail was established in 1994 as a project of the Federation of American Scientists. Since 1999, it has been operated by the International Society for Infectious Diseases.[29,33]

Currently, international ProMED-mail reports in English, Spanish, Portuguese, and Russian; French will be added in the near term, and eventually Chinese and Arabic will be added as well. Each of the non-English language programs serves a particular geographic region and covers disease news and topics relevant to the region.

ProMED-mail focuses on newly described or unknown diseases, epidemics, and outbreaks, as well as the emergence of known diseases in new areas or populations. It has given early warning of outbreaks, sometimes before official sources. ProMED-mail reports are aimed primarily at the infectious disease community around the world, including scientists, physicians, epidemiologists, public health professionals, and others interested in infectious diseases of public health importance. It also has a substantial readership among the general public.

Each day ProMED-mail staff members glean several dozen reports that may have public health significance from sources including media reports, official reports, online summaries, and subscriber submissions. (ProMED-mail does not use GPHIN as a source of reports because of funding constraints.) Initial reports are reviewed by a "top moderator"—a ProMED-mail editor or associate editor. The top moderator examines each report and rejects those that are not relevant, timely, credible, or unique. The selected reports are passed to ProMED-mail's subject area moderators, who are experts in human, animal, or plant diseases. They assess each report for accuracy and reliability, verify the source, edit the report, and add references both to the general biomedical literature and to prior related ProMED reports, as well as relevant maps and images. If a report does not include key information, or is of dubious credibility, a moderator will likely issue a request for more information or query an outside expert. Some reports are rejected or combined with other reports. Brief commentaries are added to improve clarity and supply background information and context. Reports are processed based on public health significance. Most reports are categorized as not urgent; these are copy edited and posted within 24 hours of receipt. Reports that are likely to have greater importance to public health are moved more quickly through the editorial process. Urgent reports are posted immediately. All reports that are judged to be credible are posted on the ProMED-mail website and sent to subscribers (~36,000) in approximately 160 countries. Subscribers can request condensed summaries of accumulated reports or certain types of reports (e.g., those related to plant diseases). ProMED-mail reports are reviewed daily by the WHO Global Outbreak Alert and Response Network.[34]
Region/countries served: Worldwide; reports available in English, Spanish, Portuguese, and Russian.
Funding/budget/staff: Total budget and staff size were not available. Funding is provided by the International Society for Infectious Diseases, donations from users, and grants from the Gates Foundation, the Rockefeller Foundation, Oracle Corporation, and the Nuclear Threat Initiative.

QFLU

http://www.nottingham.ac.uk/~mczqres/qflu.php
Purpose: QFLU is a surveillance system that gathers information from electronic health records of patients with influenzalike illness. It is designed to support influenza planning and response.
History and operational characteristics: Established in 2006, QFLU is the national clinical surveillance system for influenzalike illness of the Health Protection Agency in the United Kingdom. The QFLU surveillance system is designed to monitor the chronology, number, and distribution of influenzalike illness cases during annual influenza season. By daily monitoring the size and progression of an epidemic, the demographics of the affected population, and the vaccination uptake, health officials would have early warning of unusual cases and clusters of disease indicative of a severe influenza epidemic or pandemic. Distribution of vaccine and antiviral supplies, treatment guidelines, and other policy decisions would be informed by these analyses. Each day QFLU collects and analyzes National Health Service clinical data from more than 2,700 general practitioners who serve approximately 25% of the UK's population (17 million people).[35] It is the largest surveillance program of its kind in Europe.

Participating practices submit aggregated data on clinical diagnoses and prescription drugs via their clinical practice computer systems; every evening QFLU extracts and analyzes these data. Data can be analyzed by country, region, or locality of the clinical practice, but to protect patient confidentiality, the only specific patient data collected by QFLU are age and sex.

The QFLU dataset contains aggregated daily and weekly summaries of the following variables: incident cases of influenzalike illness, cumulative cases of influenzalike illness from the start of the flu season each year, high-risk patients requiring influenza vaccinations, patients receiving flu vaccinations from the start of the flu season, patients consulting a general practitioner or nurse about influenzalike illness, hospital admissions due to influenzalike illness, deaths of patients with influenzalike illness, patients prescribed influenza antiviral medications, and incident cases of pneumonia.

QFLU was created by the University of Nottingham and EMIS, the UK's source of computer systems for primary care, in collaboration with the Health Protection Agency. QFLU is closely affiliated with QRESEARCH, another automated disease surveillance system that collects real-time data on a wider variety of disease indicators, including gastrointestinal symptoms, heat stroke, and vaccine-preventable diseases. QRESEARCH covers about 450 general practices in the UK, and it is intended as a means of quickly identifying regional and national patterns on a variety of disease syndromes. Data from both QFLU and QRESEARCH are analyzed and published together in *Communicable Disease Report Weekly,* a free electronic public health bulletin created for England and Wales.[35]

Region/countries served: England, Wales, Scotland, and Northern Ireland

Funding/budget/staff: Not available

European Influenza Surveillance Scheme (EISS)

http://www.eiss.org

Purpose: The European Influenza Surveillance Scheme (EISS) collects clinical and virology data on patients with influenzalike illness from a network of sentinel physicians throughout Europe. These data are used to track the characteristics of the annual flu season and to monitor the circulating influenza viruses.

History and operational characteristics: The European Influenza Surveillance Scheme is one of 14 surveillance systems that now operate under the auspices of the European Center of Disease Control's Surveillance and Communication Program; these databases are briefly described in Appendix 1.[36] European influenza surveillance began in the 1950s. The first European surveillance network, Eurosentinel Scheme, was established in 1987 and led to the development of EISS in 1996. EISS is one of the oldest and best-funded infectious disease surveillance systems in Europe; it exemplifies many aspects of the other European disease tracking systems.

As a stipulation for membership, EISS requires participating countries to have a robust national influenza network. Each network must be comprised of sentinel sites that are nationally or regionally representative, officially recognized by the health authority in the country or region of origin, able to incorporate both clinical data and laboratory data from the same population, operational for 2 years, and able to report data on a weekly basis.[37] EISS obtains its specimens for virology from a network of sentinel physicians throughout its member countries. Sentinel physicians, including general practitioners, pediatricians, and other specialists, represent 1–5% of physicians in the country or region. Physicians take nasopharyngeal or throat swabs from patients with influenzalike illness or acute respiratory syndrome and send them to a national reference laboratory for analysis. In addition to testing the samples received from the sentinel physicians, the national reference laboratories also test samples received from nonsentinel physicians. Laboratory and clinical data are entered electronically into the EISS database; EISS members can then access these data to "make detailed clinical and virology queries."[37] During influenza season, data are collected, analyzed, and reported weekly in EISS's Weekly Electronic Bulletin. The summary includes influenza activity across Europe; during the influenza season, the EISS website receives one million visits per month.

Region/countries served: 23 countries of the European Union, and Switzerland, Norway, and Romania. Countries that contribute to EISS can be found at www.eiss.org.

Funding/budget/staff: Annual budget is approximately 1,150,000 euros (US$1.5 million), of which 42% is provided by the European Commission, 52% by in-kind support from national governments, and 6% from industry. The coordinating center, currently located in the Netherlands, has four full-time staff.

Global Influenza Surveillance Network

http://www.who.int/csr/disease/influenza/surveillance/en/

Purpose: The Global Influenza Surveillance Network is a surveillance system comprised of laboratories and coordinating centers around the world that collect and analyze clinical data and specimens from patients with influenzalike illness during influenza season.[38]

History and operational characteristics: Established in 1952, the WHO Global Influenza Surveillance Network monitors, collects, and analyzes the influenza viruses that cause seasonal flu throughout the world. These data are

used to recommend vaccine strains for seasonal flu and to identify emerging strains of influenza A virus with potential to cause a pandemic. Because of the avian influenza pandemic and increasing concerns about the potential of H5N1 to cause a human influenza pandemic, in 2004 a dedicated H5 Reference Laboratory Network was established to monitor H5N1 viruses. The WHO Global Influenza Surveillance Network works closely with the UN's Food and Agriculture Organization (FAO), the agency responsible for avian influenza virus surveillance.[14,39]

The WHO Global Influenza Surveillance Network is comprised of 116 designated National Influenza Centers and 4 designated Collaborating Centers. The WHO National Influenza Centers are located in 87 countries within the 6 WHO regions. Each year during flu season, the National Influenza Centers receive 160,000 samples from patients with influenzalike illness collected by sentinel physicians in the country or region. The Centers perform culture-based virus isolation and preliminarily characterize the isolates with standardized monoclonal antibodies.[14] The National Influenza Centers then ship the influenza viruses to one of four Collaborating Centers (located in the U.S., the UK, Japan, and Australia) for detailed genetic and antigenic analysis. The Collaborating Centers are responsible for identifying the predominant circulating viruses as well as genetic drift variants and (occasional) novel influenza viruses.

Each year in February, the WHO convenes the Collaborating Center Directors and representatives of regulatory agencies to review characteristics of the influenza A and B viruses that have been identified and characterized by the Global Influenza Surveillance Network during the previous flu season. Based on these surveillance findings, the experts recommend which virus strains should go into the northern hemisphere (in February) and southern hemisphere (in August) influenza vaccines for the coming flu season.[3] The Collaborating Centers also provide vaccine seed strains to influenza vaccine manufacturers.

Region/countries served: Global; all 6 WHO regions are served by National Influenza Centers located in 87 countries.

Funding/budget/staff: Not available

Global Polio Eradication Initiative (GPEI)

www.polioeradication.org

Purpose: The WHO Global Polio Eradication Initiative (GPEI) is a surveillance and response system dedicated to prevention and control of polio. GPEI monitors pediatric populations for cases of acute flaccid paralysis and vaccinates those who are at risk for polio.[40]

History and operational characteristics: The Global Polio Eradication Initiative was launched in the Americas in 1985. The principles of the initiative were those developed for smallpox eradication (case finding and vaccination), modified to reflect the differences in the natural history of polio. The strategy was developed by the Cuban government, who successfully used high immunization coverage and held nationwide immunization days to eradicate polio in 1962.

GPEI operates in polio-endemic areas of the world. Participating countries must actively conduct clinical surveillance for cases of flaccid paralysis in children under 15 years old.[41] GPEI field staff identifies possible clinical cases of polio, collects diagnostic specimens from patients, and sends specimens to GPEI laboratories for analysis. For quality assurance, the polio network laboratories are evaluated for proficiency and recertified every 1–2 years.

When a case of polio is identified, GPEI sponsors poliovirus vaccination campaigns. These campaigns are organized by polio surveillance officers with the assistance of trained schoolteachers and community volunteers who aid healthcare providers in the administration of oral poliovirus vaccine. During these campaigns, independent monitors document vaccination rates.

As of March 2007, four countries remain officially polio-endemic: India, Nigeria, Afghanistan, and Pakistan. However, poliovirus is highly contagious, and every clinical case is thought to represent 200 subclinical cases. Reemergence is a constant threat: Between 2003 and 2005, 25 previously polio-free countries were reinfected due to importations. As a result, GPEI remains active in a region until it is certified polio-free. Before a WHO region can be certified polio-free, three conditions must be satisfied: (1) 3 years without incident cases caused by wild poliovirus, (2) excellent certification-standard surveillance, and (3) each country in the region must demonstrate the capacity to detect, report, and respond to "imported" polio cases.[42]

Region/countries served: Global; operates in 90 countries; about a third of the current efforts are focused on Southeast Asia, and the other two-thirds are concentrated in Africa and the eastern Mediterranean.

Funding/budget/staff: WHO's budget for GPEI is US$600 million this year; the Rotary International contributes about $100 million annually to the initiative. The initiative has 145 laboratories and a staff of approximately 3,000 people.

Regional Immunization Program of the Americas

http://www.paho.org/

Purpose: The Regional Immunization Program of the Americas conducts clinical surveillance using case defini-

tions and confirmatory laboratory diagnosis to monitor the impact of national immunization programs and to identify and vaccinate at-risk populations.[43]

History and operational characteristics: In 1977, following smallpox eradication, the Pan American Health Organization's (PAHO) Expanded Program on Immunization was reorganized into the Regional Immunization Program. It originally targeted six vaccine-preventable diseases that were causing a high disease burden: polio, measles, pertussis, tetanus, diphtheria, and tuberculosis. Today, the surveillance systems and diagnostic laboratories established through the Expanded Program on Immunization and Regional Immunization Program comprise the backbone of the national immunization programs in the Americas. At-risk populations are monitored either by serology or clinical surveillance by approximately 23,000 sentinel sites throughout Latin America and the Caribbean; this surveillance information is reported to a central data collection network.[44] PAHO headquarters collects and analyzes weekly surveillance data on vaccine-preventable diseases from the Americas; this information is disseminated to Member Countries in a weekly bulletin aimed at fostering information exchange and improving vaccination programs.[40]

Polio eradication strategies, consisting of high-quality surveillance of acute flaccid paralysis and routine nationwide immunization programs, including mass vaccination campaigns, effectively reduced the number of reported polio cases from 6,653 in 1970 to 0 in August 1991.[44] The program has been credited with eliminating measles and neonatal tetanus in the Americas. The last endemic measles case reported from the Americas was in 2002. Rubella and congenital rubella syndrome are now targeted for elimination by 2010.[45]

In 1979 the Regional Immunization Program established the Revolving Fund; the fund allows PAHO to purchase vaccines, syringes, and cold chain equipment at affordable rates for Member Countries in advance of payment. The fund requires that Member Countries contribute 3% of the purchase price toward the working capital of the fund; this financing mechanism generates sufficient working capital for vaccine purchase. Most countries pay more than 95% the cost of the vaccination programs.[46]

To support efforts at the national level, PAHO posts 14 international consultants in priority countries. Their primary function is to help countries strengthen and maintain high-quality surveillance. PAHO also convenes a regional technical advisory group that provides technical and operational recommendations for improving surveillance and accelerated disease control strategies to PAHO and Member Countries.[46]

Region/countries served: Latin America, including Caribbean countries

Funding/budget/staff: Not available

Global Disease Detection (GDD) Program

http://www.cdc.gov/ncidod/global/ieip/about.htm

Purpose: The Global Disease Detection (GDD) Program is a surveillance and response program that identifies emerging microbial threats and responds to infectious disease outbreaks.

History and operational characteristics: The Global Disease Detection Program was established by CDC in 2005. The program consists of the GDD Response Network, which has internationally based Response Centers, and a CDC-based Outbreak Information Center.[47]

The GDD Response Centers, of which 18 are planned, strengthen existing capacity through improved diagnostic testing capabilities, transfer of technology, and scientific training both in national laboratories and in the WHO regional epidemiology programs. Each GDD Response Center expands infrastructure established in the Field Epidemiology Training Programs and the International Emerging Infections Programs. Currently, GDD Response Centers are operational in Kenya and Thailand. In 2006, work was started on three new Centers, in China, Egypt, and Guatemala.[48]

The GDD Outbreak Information Center is an electronic reporting system that will consolidate and analyze disease outbreak data from the GDD Response Centers as well as from surveillance systems such as GPHIN, EPI-X, ProMED-mail, the Department of Defense, the intelligence community, and the Department of State. Modeled after WHO programs, the Center will issue disease alerts and determine which outbreaks are likely to require external assistance. The information is distributed within CDC and to other U.S. government agencies as well as other domestic and international partners. In nonemergency settings, the Centers will work closely with country partners to provide requested support for outbreak investigation and response. Depending on where an outbreak is located, the associated GDD Response Centers would support a rapid response team comprised mainly of host country professionals and GOARN affiliates. During times of disease outbreaks of international public health importance, the GDD Response Centers will participate as GOARN partners under WHO's leadership.[47]

Region/countries served: Currently, two GDD Response Centers are operational, in Kenya and Thailand. Three additional Centers, in China, Egypt, and Guatemala, are being established in 2007; global, as a GOARN partner.

Funding/budget/staff: In FY2006, funds were allocated for five additional GDD Response Centers, each of which will cost approximately $10 million.

Global Emerging Infections Surveillance and Response System (GEIS)

http://www.geis.fhp.osd.mil/

Purpose: The Global Emerging Infections Surveillance and Response System (GEIS) is a surveillance and response system that links Department of Defense (DoD) laboratories, research facilities, and the military health system to facilitate rapid recognition and response to protect the health of the forces and national security.[‡49,50]

History and operational characteristics: The GEIS network was established by DoD in 1997 in response to 1996 Presidential Decision Directive NSTC-7. Within the U.S., each of the three military branches has a hub that collects disease surveillance information: the Naval Health Research Center (San Diego), the Walter Reed Army Institute of Research (Silver Spring, Maryland), and the Air Force Institute for Operational Health (Brooks City-Base, Texas). Walter Reed Army Institute of Research serves as the central hub, providing guidance and support to all DoD-GEIS global partners on disease outbreak investigations, including unusual diseases and specific clusters of disease among soldiers. It also evaluates the effectiveness of medical interventions.

GEIS conducts clinical and laboratory surveillance for emerging diseases as well as for specific diseases such as influenza and other respiratory diseases, enteric diseases (e.g., norovirus), acute febrile illness (e.g., malaria), acute hemorrhagic fevers (e.g., dengue fever), antibiotic resistant microbes resistance, and sexually transmitted diseases.

Additional domestic support comes from other military centers, including the U.S. Army Center for Health Promotion and Preventive Medicine (Aberdeen Proving Ground, Maryland), the U.S. Army Medical Research Institute of Infectious Diseases (Fort Detrick, Maryland), and the Naval Environmental Health Center (Norfolk, Virginia).

The international GEIS network is primarily conducted by five DoD overseas medical research laboratories on three continents, some of which have been operational since the 1940s:

- Armed Forces Research Institute of Medical Science (AFRMIS), Thailand
- U.S. Army Medical Research Unit, Kenya
- U.S. Naval Medical Research Unit (NAMRU)-3, Egypt
- U.S. Naval Medical Research Unit (NAMRU)-2, Indonesia
- Naval Medical Research Center Detachment (NMRCD), Peru

The laboratories in Thailand, Egypt, and Indonesia are WHO Collaborating Centers.

GEIS uses morbidity and mortality and laboratory data from the host country as well as those of U.S. military personnel stationed in the region to identify and confirm disease outbreaks. GEIS-supported laboratories have molecular- and culture-based diagnostic capabilities; each receives and analyzes samples collected from patients presenting with the syndromes of interest (e.g., influenzalike illness or hemorrhagic fever).

The NAMRU-2 Laboratory in Indonesia collaborated to establish two regional programs for global disease surveillance and response. The Early Warning Outbreak Recognition System (EWORS), established in 1998, is a hospital-based computer database used in Indonesia, Cambodia, Laos, Vietnam, and Peru to collect and analyze clinical signs and symptoms of patients seen by participating healthcare providers. The system is aimed at detecting communicable disease outbreaks early, based on identifying unusual diseases and unusual clusters of diseases (e.g., increased case rates). After healthcare providers enter patient data into the electronic EWORS system, the information is analyzed by the country's EWORS host. In Indonesia, for example, the EWORS host is the Ministry of Health's National Institute of Health Research and Development. The host then provides appropriate feedback to healthcare sites and determines if other facilities should be advised to look for similar cases. (See: http://www.science.org.au/events/indonesia/sedyaningsih-mamahit.pdf.) In 2005, the EWORS database was upgraded to facilitate the identification of influenzalike illness cases.[51]

The other program, ASEAN-Outbreak.Net, is a web-based outbreak response tool used by the Association of Southeast Asian Nations (ASEAN). Developed collaboratively with the Indonesian Ministry of Health, the tool is the official web-based platform of the ten ASEAN countries "for reporting and tracking of infectious disease outbreaks between member countries and the WHO regional offices."[50]

Communication and collaboration between WHO and the GEIS system is facilitated by several mechanisms: (1) use of an electronic communication system (e.g., websites and portals) that can be accessed by GEIS, CDC, and WHO; (2) the Naval Health Research Center (San Diego) and the Air Force Institute for Operational Health (Brooks City-Base) provide weekly U.S. surveillance information and influenza virus specimens to CDC and WHO during the annual influenza season; (3) DoD has an officer with

[‡]In 1997, DoD-GEIS piloted the syndromic surveillance program, ESSENCE, for the early detection of infectious disease outbreaks at military treatment facilities. It was based in the National Capital Region (NCR) to identify disease outbreaks caused by deliberate release of an infectious agent. The system collected diagnoses from ambulatory patients in 104 primary care and emergency clinics within a 50-mile radius of the NCR. After 9/11, ESSENCE was expanded to serve the global military health system; it currently collects syndromic data from 312 military installations.

public health training stationed at WHO in Geneva; and (4) three of the five DoD overseas laboratories provide WHO with regional influenza surveillance data and clinical specimens; in 2005, NAMRU-2 supported the identification of H5N1 from wildfowl specimens in Kazakhstan.

Region/countries served: United States (military bases), Thailand, Kenya, Egypt, Indonesia, Peru, and regions surrounding each; global, as a GOARN partner

Funding/budget/staff: The GEIS core budget is programmed in the DoD through FY2009 at approximately $11.5 million. The core budget can be supplemented to meet special threats, as was done to improve surveillance for highly pathogenic avian influenza virus.

Biological Threat Reduction Program (BTRP)

http://cns.miis.edu/cns/dc/cbw_seminars/060328.htm

Purpose: The Biological Threat Reduction Program (BTRP), formerly the Biological Weapons Proliferation Prevention (BWPP) Program, is a DoD surveillance and response program designed to enhance biosecurity and biosafety at research facilities in Kazakhstan, Uzbekistan, Azerbaijan, Georgia, and Ukraine.

History and operational characteristics: The program was established in 2003 by the DoD's Defense Threat Reduction Agency (DTRA). Using existing research infrastructure and in-country expertise as the backbone of each country's system, the BTRP is expanding those programs to include disease surveillance and response capabilities. The primary focus is diseases caused by 14 select agents that have a history of being weaponized by a state and diseases that present a pandemic threat (e.g., H5N1 avian influenza).[15]

Each host country has a network of "sentinel medical facilities," a Central Reference Laboratory, and a national response team(s) that identify, investigate, and respond to deliberate and naturally occurring disease outbreaks.[§] Clinicians at sentinel medical facilities report human cases that match the case definitions of interest (e.g., influenzalike illness, acute febrile illness, or acute hemorrhagic fever). Likewise, veterinarians report veterinary diseases of interest to the host country's Central Reference Laboratory and to the DoD. Each Central Reference Laboratory analyzes environmental and clinical samples using standardized nucleic acid detection methods with quality controlled reagents, protocols, and equipment. Laboratory information and communications with the DoD are managed with an electronic database, Electronic Integrated Disease Surveillance System (EIDSS).

If a disease outbreak caused by one of the 14 pathogens is detected or if a disease outbreak of international public health significance occurs, the closest response team travels to the site to conduct initial epidemiologic investigations and to collect additional samples for laboratory analysis. Response times vary; in smaller countries such as Georgia and Azerbaijan, a team can reach a site in one day. In a larger country like Kazakhstan, it could take longer.** For reports of less serious diseases, more information may be needed before a response team will be mobilized.

All the programs are operational, with the program in Georgia being the most proficient of the BTRP Centers. The surveillance system will be expanded to include drug-resistant tuberculosis, rabies, cholera, malaria, and other diseases of public health importance in the countries; however, these public health efforts will be supported by other sponsors.

Region/countries served: Kazakhstan, Uzbekistan, Azerbaijan, Georgia, and Ukraine

Funding/budget/staff: In FY2006, funding for the Biological Threat Reduction Program was $60 million, and over the next 5 years, the U.S. intends to spend approximately $400 million on the program. The BTRP system is designed to be self-sustaining after an agreed-on start-up period.

Outbreak Alert and Verification System

http://www.who.int/csr/don/en/

Purpose: The Outbreak Alert and Verification System is part of WHO; it is designed to assess the relevance of unconfirmed disease outbreak reports to international public health and, if appropriate, to seek further information from the affected country or region. If the report is verified and if the outbreak is still considered to be important to international public health, the information is communicated to the Global Alert and Outbreak Response Network (GOARN) of international partners.[24]

History and operational characteristics: Since it was established in 1997, the Outbreak Alert and Response Operations Team has met daily to review formal and informal disease outbreak reports received in the preceding 24 hours. Formal reports originate from the ministries of health of the involved country(s), WHO Regional and Country Offices, other UN agencies, and WHO Collaborating Centers. Sources of informal reports include nongovernmental organizations, international organizations, other WHO partners, and media services like GPHIN and ProMED-mail. This event alert and verification system continuously

[§]Field stations used in the former Soviet Anti-Plague System or the Sanitary Epidemiological System are often assessed for use as BTRP sentinel sites.

**Because of the size of Kazakhstan, DTRA is planning to establish a number of outbreak response posts throughout the country. To determine the appropriate locations of these outbreak response posts, DTRA convened an integrated panel of experts to decide their placement.

and systematically assesses reports of suspected disease outbreaks around the world. WHO Regional and Country Offices are tasked with verifying reports in collaboration with the national health authorities. The involved country(s) may request WHO's assistance for the epidemiologic investigation and verification of the report

The Outbreak Alert and Response Operations Team carries out preliminary risk assessments on the incoming information using International Health Regulations (2005) criteria to determine if the reported outbreak might be of international public health importance if it were confirmed to (1) be an unknown disease or unexpected event, (2) have the potential for spread beyond national borders, (3) cause a serious health impact or high rates of morbidity and mortality, and (4) pose significant risk of international restrictions on trade or travel. Seven specific diseases—smallpox, plague, yellow fever, cholera, poliomyelitis due to wild-type poliovirus, human influenza caused by a new subtype, and SARS—require immediate assessment and notification under IHR 2005.

All reports of disease outbreaks with potential international public health impact are compiled on the "Daily List," a list of monitored information and activities about unverified reports that is a confidential working document of WHO Geneva. The six Regional Offices of WHO are responsible for tracking outbreak reports that occur in their regions.

Once the involved country receives a request to investigate a disease outbreak, the report is added to the Outbreak Verification List (OVL). The median time between receiving an unconfirmed report of a disease outbreak of international public health concern to its appearance in the OVL is 3 days. Since the events listed on the OVL have not been verified, the list is not available to the public.

If a disease outbreak is verified, and if it is still considered to be of international public health concern, the report will be posted in Disease Outbreak News on the WHO website (http://www.who.int/csr/don/en/), and it will be included in the Outbreak News section of the WHO *Weekly Epidemiological Record*.

According to the provisions of IHR 2005, in the near future, the OVL will be replaced with web-based technology for communications between IHR National Focal Points (an institution designated in the Member State to deal with IHR-related issues) and WHO.

Region/countries served: Global
Funding /budget/staff: Not available

Epidemic and Pandemic Alert and Response (EPR)

http://www.who.int/csr/en/

Purpose: The Epidemic and Pandemic Alert and Response (EPR) is a verification and response program that monitors and facilitates effective response to outbreaks of 15 infectious diseases: anthrax, avian influenza, viral hemorrhagic fevers (Crimean-Congo, dengue, Ebola, Lassa, and Marburg), Rift Valley fever, hepatitis, influenza, meningococcal disease, plague, SARS, tularemia, and yellow fever.

History and operational characteristics: Overall, EPR has six primary functions:

1. To support Member States in developing national capabilities for epidemic preparedness and response in the context of IHR 2005, including laboratory capabilities and early warning alert and response systems;
2. To support national and international training programs for epidemic preparedness and response;
3. To coordinate and support Member States for pandemic and seasonal influenza preparedness and response;
4. To develop standardized approaches for readiness and response to major epidemic-prone diseases (e.g., meningitis, yellow fever, plague);
5. To strengthen biosafety, biosecurity, and readiness for outbreaks of dangerous and emerging pathogen outbreaks (e.g., SARS, viral hemorrhagic fevers); and
6. To maintain, improve, and expand a global operational platform to support outbreak response and support regional offices in implementation at the country and regional levels.

The EPR also publishes guidelines and manuals on the surveillance and control of epidemic-prone diseases. Resources include guidance on how to assess surveillance systems; maps to support public health activities at the district, national, regional, and global levels; videos for training health professionals and raising awareness of the diseases and their treatments; software to help analyze and compare data; and databases that track the occurrences of diseases over time.

Region/countries served: Global
Funding/budget/staff: Not available

Global Outbreak Alert and Response Network (GOARN)

http://www.who.int/csr/outbreaknetwork/en/

Purpose: GOARN is a verification and response program; it is a voluntary technical partnership of approximately 140 institutions coordinated by WHO to support countries in disease outbreak investigation and response, primarily through the deployment of multidisciplinary teams. GOARN's mission is rapid identification and/or confirmation and effective response to disease outbreaks of international public health importance.[24,26,52,53]

History and operational characteristics: Formalized in 2000, GOARN's international outbreak response teams are assembled and mobilized to countries where a disease out-

break is occurring. The teams offer support to the national health authorities for effective coordination and outbreak control activities. The multidisciplinary teams offer expertise in social mobilization, epidemiology, clinical diagnosis and management, infection control, laboratory evaluation, veterinary public health, influenza virology, operational coordination and logistics, outbreak communications, and field information management. The teams also provide advice on the use of field investigation kits; personal protective equipment (PPE); therapeutics and vaccines; stockpile management, including storage and distribution of laboratory supplies, reagents, and diagnostic kits; and international sample transport protocols and equipment.

International response to a potential disease outbreak begins at the time a WHO regional office requests that an involved country investigate and verify a report of a disease outbreak. If the disease outbreak is confirmed, WHO assists the involved country in conducting a risk assessment on the humanitarian consequences, the potential impact on international travel and trade, and the need for international support. At this point, the country may request the aid of WHO/GOARN.

Regions/countries served: Global

Funding/budget/staff: WHO provides administrative support for GOARN, which is comprised of a small secretariat including a project manager, support for a steering committee, and an operational support team.

The Nuclear Threat Initiative's WHO-NTI Global Emergency Response Fund provides WHO with a renewable $500,000 grant to enable WHO to immediately mobilize GOARN teams to areas affected by outbreaks while funds to respond to the outbreak are solicited from World Health Assembly member countries.

The annual budget for GOARN's disease outbreak response activities was not available.

Preparedness and Response Unit

http://www.ecdc.eu.int

Purpose: The Preparedness and Response Unit is a multilateral surveillance and response program of the European Centre for Disease Control (ECDC) that supports European Union (EU) Member States in assessing, investigating, and responding to emerging threats in Europe; the Unit is also a GOARN partner.

History and operational characteristics: Established in 2005, the Preparedness and Response Unit is in charge of outbreak assessment and response. It has three critical capabilities: epidemic intelligence analysis, outbreak response and preparedness, and capacity strengthening. The unit gathers disease outbreak information from official (e.g., national health officials) and unofficial sources (e.g., media reports) and verifies disease outbreak reports through independent sources before entering information into a computerized threat-monitoring database, the Early Warning and Response System. The European Centre for Disease Control uses the Early Warning and Response System to notify EU Member States of regional public health threats and to coordinate appropriate response measures. If there is a need for European coordination or international assistance, or if there is a risk of an outbreak spreading throughout Europe, the unit will issue an alert to EU Member States.

The unit works in concert with the European Commission Health Threat Unit to ensure that outbreak response is handled at the European Union level; it can dispatch teams within Member States to support national health authorities. For outbreaks outside the EU, the unit is a WHO GOARN partner and may function in that capacity in response to a request from WHO.

Region/countries served: European Union; global, as a GOARN partner.

Funding/budget/staff: Not available

Assessment of the Impact of a Proposed Solution: Rapid Diagnostic Tests

The impact of rapid, simple, affordable diagnostic tests that are appropriately sensitive and specific was assessed using the notional scheme. Each of the four functions and the footnoted caveats were taken into consideration (see Figure 1). The potential contributions of such tests are summarized for each of the four functions (Figure 3). Such tests improve surveillance functions when used for preliminary screening because presumptive positive test results are an impetus to seek health care. When such tests are used in point-of-care settings, the results inform (1) confirmatory testing at the central or regional lab; (2) medical treatment, including vaccination of the patient and contacts; (3) infection control in the healthcare setting; (4) necessary follow-up care; and (5) local immunization programs for vaccine preventable illness.

Reliable diagnostic test results (1) increase the credibility of the disease outbreak report; (2) facilitate the rapid verification of the seven specified diseases (IHR 2005); (3) reduce requests for verification of reports and the risk of negative impact on trade and travel that could occur if the epidemiologic investigation became public knowledge; and (4) facilitate effective use of the WHO algorithm. These tests have a key role in verification and response to an epidemiological outbreak. Affected countries would use the tests to screen people and to guide confirmatory testing at the central/regional level. The tests will facilitate mapping the extent of the outbreak and inform requirements for outbreak containment. Diagnostic tests will also support

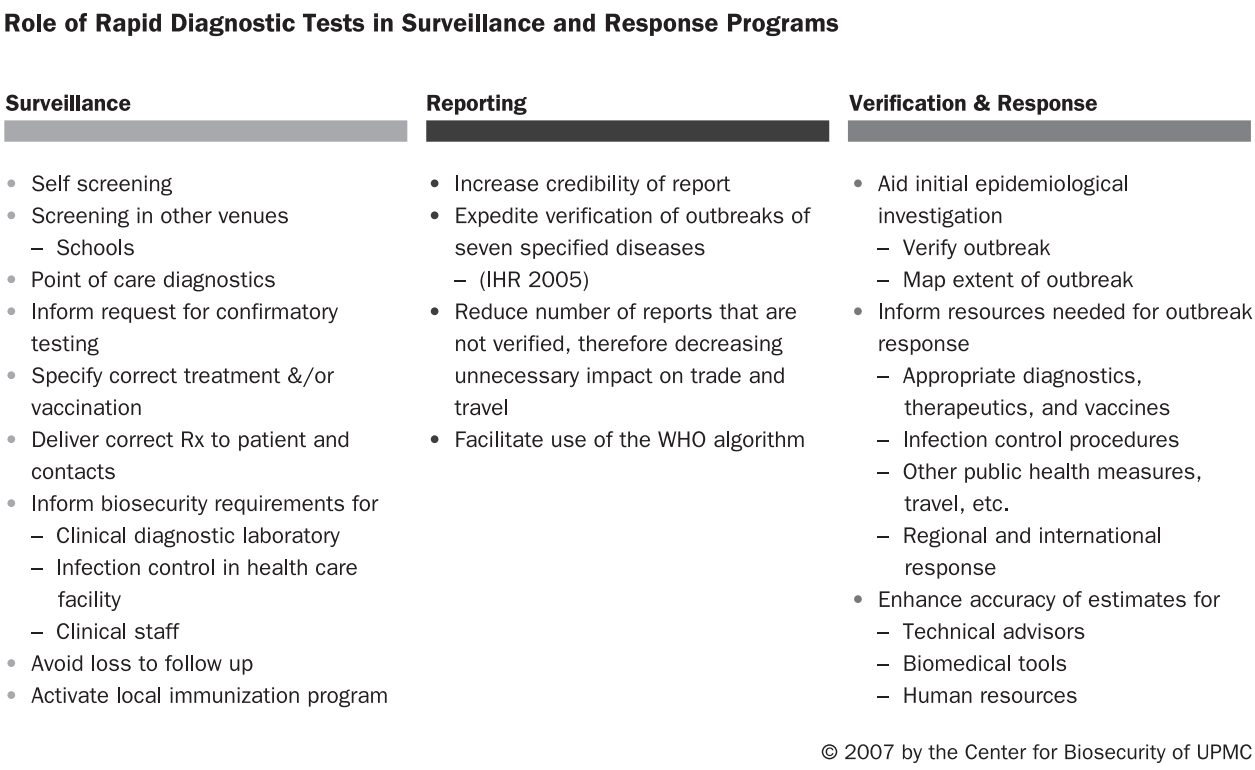


Figure 3. All of the functional components—surveillance, reporting, verification, and response—are likely to be enhanced with the use of appropriate rapid diagnostic tests.

situational awareness at the local, regional, and/or international levels.

Notable Practices and Achievements

GPHIN and ProMED-mail are chief sources of reports sent to WHO. GPHIN's global coverage is extensive; this is primarily attributable to evaluation of news media in seven languages. Between 1998 and 2001, WHO's Outbreak Alert and Verification System confirmed 578 outbreaks, of which 56% were initially picked up by GPHIN.

ProMED-mail uses in-country infectious disease experts to improve the credibility of outbreak reports. The experts review preliminary reports and often request additional information about suspected outbreaks. ProMED-mail was the source of the first SARS report and a recent outbreak of yellow fever in Brazil.

The ProMED-mail program also is a model for an affordable surveillance system that may be suitable for countries with limited resources. The basic requirements are modest: a university-based server, a website manager, and the personal computers of the subject matter volunteers. Since 1994, national ProMED-mail systems have been established in Brazil, the Netherlands, and South Korea. However, the governments of many countries are reluctant to implement a national version of ProMED-mail, because subscriber-based input may circumvent official reports of the ministry of health.[29]

The time interval between the beginning of an epidemic and recognition of the epidemic affects the magnitude of the epidemic and, consequently, the magnitude of the response required to contain it. Real-time surveillance theoretically reduces the time interval between outbreak and detection. QFLU is a surveillance program that approximates a real-time (24-hour) clinical surveillance and reporting capability. This time frame is possible because of the National Health Service electronic record system. QFLU uses analytical tools to monitor the timing, magnitude, and spread of seasonal and/or pandemic influenza. This report, updated daily, contributes to situational awareness and informs decisions about use of drugs, vaccines, and infection control measures. A pilot study was conducted to measure the robustness of QFLU's case-definition–based clinical diagnosis. Laboratory results of nasal swabs from patients with influenzalike illness indicated that, during seasonal flu, the clinical diagnosis of influenzalike illness is a sensitive indicator of influenza (A. Cooper, personal communication, Fall 2006). QFLU is designed to protect confidentiality by collecting only patient age and sex.

Annual influenza vaccination reduces morbidity, mortality, and healthcare costs; the effectiveness of influenza vaccines is, in large part, attributable to the Global Influenza Surveillance Network (GISN). Information about circulat-

ing influenza viruses is the basis for strain selection for annual flu vaccines. The network has developed and adheres to rigorous standards, exemplified by those established by the European Influenza Surveillance Scheme (EISS). These standards of operation contribute to the reliability of vaccine strain selection and also facilitate recognition of unusual clusters of influenza cases and identification of strains with pandemic potential.

In response to the avian influenza pandemic, GISN has worked to integrate human and veterinary surveillance. Designated H5N1 laboratories conduct comparative analysis of animal, mammalian, and human strains. GISN also has supported H5N1 disease outbreak response capabilities by aiding GOARN partners in epidemiologic investigations in affected countries. GISN collaborates with the U.N.'s Food and Agriculture Organization and other expert groups to (1) develop operational definitions of a cluster of cases of influenza attributable to human-to-human transmission; (2) recommend strategies to prevent transmission of H5N1 from poultry to humans; and (3) improve H5N1 surveillance capabilities in affected and vulnerable countries. GISN's laboratory infrastructure is well established in 87 countries and could be expanded to include other zoonotic and emerging diseases with potential impact on international public health.

The Global Polio Eradication Initiative and the Regional Immunization Program of the Americas illustrate surveillance and response programs that use a case-definition/ laboratory confirmation–based surveillance system linked to immunization programs to control vaccine-preventable illness. The GPEI program has made a significant impact on the prevalence of polio throughout the world. This is remarkable given that the majority of polio infections are asymptomatic. Two practices contribute to this success: GPEI has a quality assurance program that evaluates laboratories for proficiency and recertifies them every 1–2 years, and the program achieves high vaccination rates (~90%) during immunization campaigns.

Recently, polio network laboratories in 125 countries have expanded the scope of epidemiologic and laboratory testing of diseases to other viruses including the pathogens that cause measles, yellow fever, hemorrhagic fevers, meningitis, Japanese encephalitis, and SARS. Since the emergence of H5N1, GPEI teams in Nigeria and India have been involved in epidemiologic investigations of avian influenza.[54]

The Regional Immunization Program of the Americas targets vaccine preventable illnesses that affect the health of the public. The program has created national infrastructure for surveillance and response (23,000 sentinel sites throughout Latin America and the Caribbean) and a central data collection network to enhance regional cooperation, which could be expanded to cover other emerging diseases. The Revolving Fund is an integral part of the success and sustainability of the PAHO program, because it guarantees adequate supplies of affordable vaccines. Another key component of the longevity and success of the program is the in-country capacity building, which is facilitated by a small team (14) of international consultants and a regional technical advisory group.

Three programs illustrate systems focused on detection of emerging diseases and improvement of regional capacities for surveillance and response: the Global Disease Detection Program (GDD), the Global Emerging Infections Surveillance and Response System (GEIS), and the Biological Threat Reduction Program (BTRP).

The GDD program is strengthening infrastructure in host countries by building on established CDC programs. Improvements are planned in applied epidemiology and public health practice and better integration of disease surveillance and outbreak response capabilities, including augmenting molecular diagnostic capabilities. GEIS includes laboratories that have molecular- and culture-based diagnostic capabilities that have supported analysis of H5N1 strains and the infectious disease isolates associated with the 2004 Indian Ocean tsunami. GEIS also has collaborated to strengthen regional surveillance network capabilities. The Early Warning Outbreak Recognition System is used by Indonesia, Cambodia, Laos, Vietnam, and Peru. ASEAN-Outbreak.Net is used by 10 Asian countries and the WHO regional offices; usage has increased from just over 1,000 unique users in May 2003 to 15,000 in May 2004 to 23,000 in 2005.[50]

BTRP has standardized reagents, protocols, methods, and performance metrics that contribute to accurate reporting, verification, and rapid, effective response to outbreaks of emerging diseases. The program also has begun to strengthen linkages between human and veterinary programs; one of the centers investigated wild bird die-off near the border of Kazahkstan and isolated H5N1 virus from affected birds. To better serve the public health needs of the host countries, BTRP will be expanded in collaboration with other co-sponsors to include drug-resistant tuberculosis, rabies, cholera, malaria, and other diseases.

The Epidemic and Pandemic Alert and Response (EPR) program provides international guidelines and manuals including, but not limited to, protocols to assess surveillance systems, software to help analyze and compare data, and databases to track the occurrences of diseases over time for 15 epidemic-prone diseases. Such standards provide benchmarks for early detection and effective response to disease outbreaks.

Outbreak verification and response were represented by three international programs: WHO's Outbreak Alert and Verification System, the European CDC's Preparedness and Response Unit, and WHO's Global Outbreak and Alert Response Network (GOARN).

The Outbreak Alert and Verification System compiles the Outbreak Verification List (OVL). This confidential weekly report is sent electronically to a selected group of public health professionals around the world. The individuals who receive the OVL communicate directly with WHO staff about the potential ramifications of the putative disease outbreaks and necessary epidemic responses. The outbreak reports on the OVL are unverified, so it is not made available to the public; this precaution limits any unnecessary impact on trade and travel in instances where the outbreak report is not confirmed or not considered to be of international public health significance.

The European Preparedness and Response Unit has strengthened regional coordination in Europe and includes non-EU member countries. In terms of strengthening Member States' capacities for outbreak investigation and response, the unit's training program, European Programme for Intervention Epidemiology Training, has trained approximately 130 European epidemiologists in the past 10 years.

Since 2000, WHO/GOARN has responded to more than 50 outbreaks worldwide.[25] The SARS outbreak of 2003 was the first time GOARN teams responded to an outbreak of an unknown infectious disease.[2] During the first 6 months of 2006, WHO/GOARN mobilized more than 70 operational interventions in response to avian influenza (AI) outbreaks and human transmission.[55]

CHALLENGES

The challenges to effective global surveillance and response to human disease outbreaks reflect deficiencies in (1) health infrastructure; (2) scientific methods and concepts of operations of infectious disease surveillance programs; (3) human, technical, and financial resources; and (4) international policies.

Health Infrastructure

- Healthcare facilities provide the primary opportunity for detecting cases of unusual diseases or unusual clusters of disease, but healthcare facilities are absent or inadequate in resource-limited countries in Africa, Asia, and other parts of the world. Consequently, these countries do not have adequate domestic disease detection or response capabilities.[56]
- The absence of health infrastructure in resource-limited countries creates gaps in coverage in regional surveillance systems. The result is a porous patchwork of surveillance systems that is exacerbated by differences in focus, approach, intended audience, and resource base and by inadequate integration and poor coordination between surveillance systems.[1]
- Establishing de novo healthcare infrastructure is difficult. Because agencies in developed countries often have prerequisites for investing in infectious disease surveillance and response systems, there are few examples of investments in developing countries that have simple or no health infrastructure.
- With the exception of H5N1, there is little coordination or harmonization between human and veterinary sectors of the infectious disease health infrastructure.[57,58]

Methodology

- There is no consensus on the preferred methodologies, performance characteristics, or outcome measures for surveillance programs.[59–63]
- There are no clear measures of effectiveness or cost-effectiveness of infectious disease surveillance systems. With the exception of those systems that have as their goals disease eradication or control of vaccine-preventable illness, it is difficult to assess the contributions of the surveillance systems.[64,65]
- Given current surveillance methods, it is doubtful that infections that spread rapidly (e.g., influenza) or that spread silently (e.g., HIV infection) can be detected before they are widely disseminated. Regional and/or international outbreak responses may be the first response in containment of these infections.[26,66]

Technical Resources

- Diagnostic tests are essential for rapid screening and confirmatory diagnosis of sick patients in primary care and/or emergency care facilities. Either these tests do not exist for most diseases, or they are too expensive and/or too technical for use in resource-limited health infrastructures. In the absence of an etiologic diagnosis, the opportunity for surveillance and response—including proper medical care treatment, appropriate vaccination, and use of effective infection control procedures—will be lost.[67] Despite the essential role of these tests in diagnosis and response, the resources available for the development, manufacturing, and distribution of these diagnostic tests are inadequate. All components of surveillance and response would be enhanced with these tests (see Figure 3).
- The global communication networks necessary to support infectious disease surveillance systems are inadequate. Countrywide deficiencies in the phone and internet systems weaken surveillance, reporting, outbreak investigation, and response.[68] Even where electronic reporting systems are available, they are often not used regularly for disease surveillance, in part because information technology personnel are inadequately trained and funded.[69]

- The accuracy of electronic surveillance systems that use media sources is constrained by both the quality of news reports and the completeness of news coverage. In addition, analytical methods and the number of subject-matter analysts available to assess the credibility of the reports vary across the systems.
- "Real-time" surveillance (used here to mean data available in 24 hours or less) is not possible in most systems, although it has been conducted at special events such as the G8 Summit or the Democratic National Convention.[70,71] The French Communicable Diseases Computer Network and the European Influenza Surveillance Scheme collect and analyze data at least once per week.[72] The QFLU program, piloted in the 2006 influenza season, has the potential for daily reporting; however, that system uses depersonalized data collected from electronic health records, a data source that is not available in most countries.

Financial and Human Resources

- The new IHR 2005 provides a legal framework for global surveillance of and response to human disease, but there are no funds available for implementation. Many resource-limited countries do not have the monies available to establish surveillance and response systems.
- There is no strategic plan to raise the financial resources required for implementing the revised IHR 2005 at the country level. Without identified financial resources to acquire needed technical and human resources, the plans for implementing IHR at the country level are unlikely to be realistic.
- The designated human and financial resources of WHO are inadequate to fulfill the expanded responsibilities stipulated in IHR 2005. The dependence of WHO on volunteer donations and temporary staff weakens the potential of IHR 2005.
- The Global Outbreak Alert and Response Network's operating budget is not part of WHO's core budget. Currently, a private philanthropic organization, the Nuclear Threat Initiative, provides some financial resources for initial outbreak assistance. However, all funds required for international response to disease outbreaks are donated at the discretion of World Health Assembly Member States.[8]

Policy

- Perceived economic consequences due to disruption of trade and travel caused by disease outbreaks deter reporting and delay verification.[23] Although health-related regulatory provisions among WHO, the World Trade Organization (WTO), the International Civil Aviation Organization (ICAO), and the Food Agriculture Organization (FAO) are being coordinated to decrease the economic risk to countries that report disease outbreaks, the economic impact of the SARS epidemic suggests that additional measures are necessary.[9,73]
- IHR 2005 requires that all countries take responsibility for reporting disease outbreaks; this will be a source of friction between the countries involved in bilateral agreements unless memos of understanding are revised and standard reporting procedures are developed between host and sponsoring countries.[73]

SUMMARY

Although an ad hoc global surveillance and response system "worked" in 2003 to contain the SARS outbreak, many experts doubt that it will be able to contain outbreaks of highly contagious diseases, such as pandemic flu, or diseases that spread silently, such as West Nile viral encephalitis. Our findings fully support these concerns.

Achieving effective global surveillance and response capabilities depends on cultural acceptance of two key concepts: global mindsets and global resources. These concepts reflect the worldwide nature of the threat of emerging diseases and the erosion of geographic, cultural, and social barriers that have historically functioned to deter the spread of infectious diseases. If disease outbreaks of potential international public health importance cannot be detected and contained in all places, it is likely that they will have an impact on global health security and on global economic stability. The most compelling example of this is the global spread of HIV/AIDS in the past three decades. Containment of global disease outbreaks will require all nations to work in partnership and to pool resources.

In a 2006 IOM report, the primary prerequisite for creating effective infectious disease control programs was identified as global mindsets. This concern for the absence of global mindsets was reiterated in the 2007 Oslo Declaration on Global Health.[74] Global mindsets are a prerequisite for international policies; long-term global collaborations; larger, more flexible financial consortia; and innovative approaches.[1]

The second concept is global commitment of necessary financial, human, and technical resources. A realistic funding plan must be developed and implemented to build, strengthen, and sustain local health infrastructure. It must include the resources required to train health providers and for the development and distribution of diagnostic tests that are affordable and appropriate for use at the local level. It also means that financial commitments to effective programs for vaccine-preventable illnesses such as polio and rubella must be sustained and expanded globally so that effective health infrastructure can be used to avert diseases

that are vaccine-preventable while contributing to surveillance and response capability for rapid containment of emerging infectious disease threats.[50]

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APPENDIX 1

European Center for Disease Control Disease Surveillance Systems‡

Project/ Program Name	Headquarters Location	Date Established	Mission/ Goal
Basic Surveillance Network (BSN)	Stockholm, Sweden	2000	To collect data on numbers and incidences from national databases and gather them in one place. Provides access to basic descriptive epidemiologic data for all listed diseases and European countries.
European Influenza Surveillance Scheme (EISS)	Netherlands	1996	To monitor the annual flu epidemic and collect patient samples for virology to inform vaccine strain selection.
European Antimicrobial Resistance Surveillance System (EARSS)	Netherlands	1999	To maintain a comprehensive surveillance and information system on the prevalence and spread of major invasive bacteria with clinically and epidemiologically relevant antimicrobial resistance in Europe.
European Centre for the Epidemiological Monitoring of AIDS (EuroHIV)	France	1984	To coordinate the surveillance of HIV/AIDS in the WHO European Region (52 countries); objectives include making international comparisons, assessing trends, characterizing affected populations, predicting disease burden, and evaluating surveillance methods.
European Union Invasive Bacterial Infections Surveillance Network (EU-IBIS)	London, England	1999	To improve the epidemiologic information on invasive disease caused by *N. meningitides* and *H. influenzae* within the EU; to improve the laboratory capacity by standardizing methods; to evaluate the impact of vaccination on the epidemiology of *N. meningitidis* and *H. influenzae*; to compare the impact of vaccination with conjugate vaccines produced by different manufacturers and according to different schedules.
European Network for Diagnostics of "Imported" Viral Diseases (ENIVD)	Berlin, Germany	1998	To improve diagnosis of "imported" and emerging virus infections.
Surveillance of Tuberculosis in Europe, WHO Collaborating Centre (EuroTB)	France	1996	To improve public health surveillance of tuberculosis in Europe and to standardize tuberculosis surveillance methods.
European surveillance network for vaccine preventable diseases (EUVAC.NET)	Copenhagen, Denmark	1999	To conduct epidemiologic surveillance and control of vaccine-preventable diseases in the European community.
European Working Group for Legionella Infections (EWGLI)	London, England	1986	To improve knowledge and information on the epidemiologic and microbiologic (clinical & environmental) aspects of legionnaires' disease. Achieved through international surveillance and improved diagnostics, management, and treatment methods.
International surveillance network for the enteric infections Salmonella and VTEC 0157 (Enter-net)	London, England	1997	To maintain and develop international laboratory-based surveillance of the major enteric bacterial pathogens; maintain national reference services; monitors epidemiologic trends, disseminates information on potential international incidents, and responds to international outbreaks of food-borne pathogens.

Hospital in Europe Link for (Nosocomial) Infection Control Surveillance (HELICS)	Lyon, France	1995	To collect, analyze, and disseminate valid data on the risks of nosocomial infections in European hospitals.
The European and Allied Countries Collaborative Study Group of CJD, plus the Extended European Collaborative Study Group of CJD (EUROCJD, NEUROCJD)	Edinburgh, Scotland	1993 (EUROCJD) 1998 (NEUROCJD)	To identify trends in the incidence of CJD; to assess putative risk factors for CJD, including past medical history, occupation, and diet; to study the clinical pathology of CJD variants; to study the molecular biology of CJD with specific reference to genetic factors that influence susceptibility to disease.
Inventory of Resources for Infectious Diseases in Europe (IRIDE)	Rome, Italy	1997, renewed for expansion in 2000	To provide information on resources and contact points to communicable diseases in the European Union; to provide a computerized source of information for the Member States for the control of communicable diseases; to provide internet access of the database; to provide continuous updates to become Member States of the European Union; and to provide the structure for adding new country-specific databases.
European Programme for Intervention Epidemiology Training (EPIET)	Stockholm, Sweden	1995	To provide training and practical experience in intervention epidemiology for surveillance and control of communicable diseases in the European Union (EU). To strengthen the surveillance of infectious diseases in EU member states and at the community level; to develop response capacity at national and community levels to meet communicable disease threats through rapid and effective field investigation and control; to develop a European network of public health epidemiologists using standard methods.
European Surveillance of Sexually Transmitted Infections (ESSTI)	London, England	2001	To improve collaboration (multidisciplinary, internetwork, and multiagency), build capacity, and facilitate robust dissemination of information on sexually transmitted infections to inform public health policy and planning across European Union partners.

‡*Source:* Lenglet A, Hernandez Pezzi G. Comparison of the European Union Disease Surveillance Networks' websites. *Euro Surveill* 2006 May;11(5):119–122.