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CHAPTER 14

Global Surveillance for Emerging Infectious Diseases

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INTRODUCTION

Despite advances in science, technology, and medicine that have improved disease prevention and management, endemic and emerging infectious diseases continue to pose threats to domestic and global health. Established diseases such as malaria, tuberculosis (TB), and human immunodeficiency virus (HIV) infection still proliferate, fueled in part by antimicrobial resistance.[1] The increasing speed and volume of international travel, migration, and trade create new opportunities for microbial spread, and the prospect of a deliberate release of pathogenic microbes underscores the importance of preparedness to address the unexpected.[2,3] The examples of severe acute respiratory syndrome (SARS), a previously unknown disease that spread rapidly around the world in 2003, and pandemic H1N1 influenza in 2009 (***Fig. 14.1***), illustrate the vulnerability of the global community to new microbial threats and highlight the need for increased vigilance and strengthened response capacity.[4,5]

Concerns about global health security led World Health Organization (WHO) Member States to formulate and adopt the revised International Health Regulations (IHR) in 2005.[6] The new requirement for IHR State Parties to develop and maintain defined core capacities for national surveillance and response highlights the importance placed on early recognition of disease events so that measures can be promptly taken to control the threat at its source before the disease can spread to other countries. Furthermore, countries that can provide assistance must help countries that lack available resources. Effective global surveillance requires that each country have a strong national surveillance system.

Recent domestic challenges have included the introduction of West Nile encephalitis[7,8] and monkeypox[9] into the United States; the anthrax episodes of fall 2001;[10] multistate outbreaks involving contaminated food products[11,12] and pandemic H1N1 influenza.[13] Internationally, public health officials have faced the emergence of Nipah virus[14] and SARS,[15] the intensified global spread of dengue,[16,17] Ebola and Marburg outbreaks of unprecedented magnitude,[18,19] the direct avian-to-human transmission of H5N1 influenza,[20,21] and the spread of chikungunya virus from Africa to islands in the Indian Ocean, Asia, and Europe.[22] The 2009 H1N1 influenza pandemic originated in Mexico, but the virus was identified first from cases in the United States.[13] Each of these examples illustrates the global implications of local problems, the role of strong health intelligence networks in addressing emerging infections, and the importance of data on the background rate of diseases in recognizing unusual disease events.[23]

PUBLIC HEALTH SURVEILLANCE

Public health surveillance is the continuous analysis, interpretation, and feedback of systematically collected information used to inform public health decision making.[24] Timely community health information in the hands of trained experts is the foundation for recognition of threats to health. To intervene successfully, disease surveillance systems need to provide a continuous, accurate, and near real-time overview of a population's health. Surveillance systems must be sensitive in terms of their ability to detect outbreaks and other changes in community health status over time, and they must be flexible in adapting novel diagnostic technology to changing health intelligence needs. Given the increasing pace of international travel and globalization and the threat of intentional outbreaks, surveillance activities need to extend beyond the monitoring of disease burden to include the capacity to quickly recognize unusual, unexpected, or unexplained disease patterns. Because many emerging infectious agents are zoonotic,[25] it is also important to integrate veterinary disease reporting networks into systems that monitor diseases of humans, as emphasized by the One Health Initiative.[26]

Astute clinicians and microbiologists are essential for early detection of threats. In the United States, surveillance for notifiable diseases is conducted by state and local health departments, which receive reports from physicians, nurses, and laboratorians who are often the first to observe and report unusual illnesses or syndromes. States voluntarily report nationally notifiable diseases to the Centers for Disease Control and Prevention (CDC) through a standards-based system for collecting and sharing electronic disease reports from health care providers within local health jurisdictions to state and federal public health authorities. In addition to these parameter-based systems, clinicians and state epidemiologists can also contact CDC directly to report disease events if urgent notification is appropriate or if the event is unusual.

Starting in 1994, CDC launched a two-phase initiative to strengthen domestic capacity to respond to the dual threats of endemic and emerging infections. The publication of two strategy documents[27,28] led to the launching of new surveillance initiatives, including the Emerging Infections Program (EIP), a national network for population-based surveillance and research.[29] Several provider-based sentinel surveillance networks were established in collaboration with emergency department physicians, infectious disease clinicians, and travel medicine specialists to provide early warning of events that might be missed by public health surveillance. Additional enhancements to the surveillance effort include development of the National Molecular Subtyping Network for Foodborne Disease Surveillance (PulseNet) as an early warning system for foodborne diseases, the Gonococcal Isolate Surveillance Project (GISP) to monitor antimicrobial resistance in *Neisseria gonorrhoeae*, strengthened surveillance for emerging diseases (e.g., West Nile encephalitis, seasonal and pandemic influenza), and surveillance for outbreaks that might be due to acts of bioterrorism.

CDC also works in partnership with WHO, ministries of health, foundations, development agencies, and other federal agencies to promote national, regional, and international disease surveillance. Recognition of the global nature of the emergence and spread of infectious diseases stimulated the development of a strategy focused on CDC's efforts to enhance global capacity for disease surveillance and outbreak response[30] focusing on six priority areas for protecting domestic and global health, among which are global initiatives for disease control, international

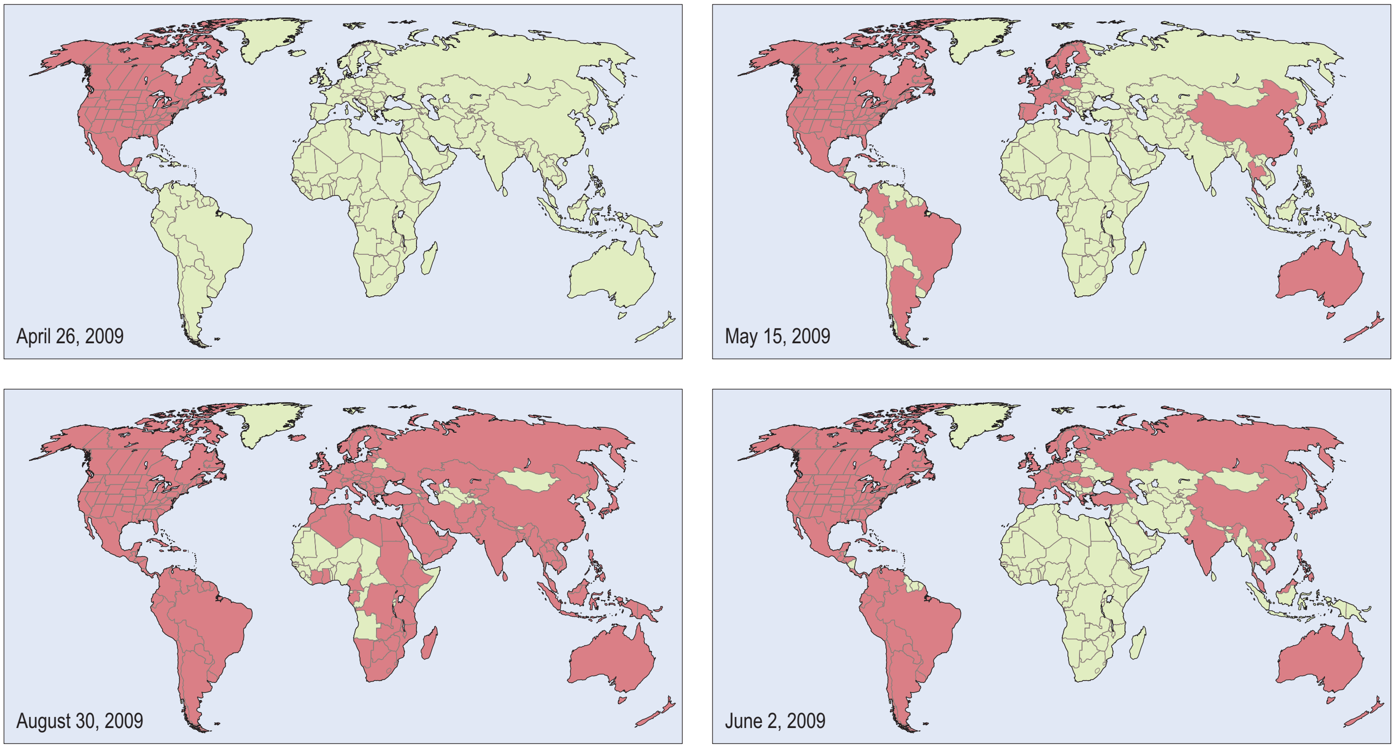

Figure 14.1 Countries with laboratory-confirmed pandemic H1N1 influenza infections – April 26, 2009 to August 30, 2009. (Source: WHO and ministries of health.)

outbreak assistance, and a global approach to disease surveillance. CDC's international activities include creation of the Global Disease Detection program (see below), US–Mexico Border Infectious Disease Surveillance (BIDS) system, development of GeoSentinel, and provision of technical assistance to regional disease surveillance networks in Africa, Asia, Latin America, and the circumpolar regions of Canada and Europe, as well as to WHO's disease-specific global networks.

WHO manages global disease surveillance and response through a composite of partnerships and networks for gathering, verifying, and analyzing international disease intelligence, mainly to support global and regional efforts to eradicate certain diseases, such as poliomyelitis, and to protect the global community against diseases with pandemic potential. The oldest of these networks is the global influenza surveillance network, which was established more than 50 years ago and has served as the prototype for the design and implementation of other systems (see below).[31]

To respond to the increasing number of emerging and rapidly spreading infectious diseases, WHO has developed a global "network of networks" that links local, regional, national, and international networks of laboratories and medical centers into a mega-surveillance network for early warning and response.[32] Formal partners include ministries of health, WHO Collaborating Centers, WHO country and regional offices, and international military groups such as the Global Emerging Infections System of the US Department of Defense.[33]

Event-based outbreak reports are also received from non-governmental organizations, relief workers, private clinics, individual scientists, and public health practitioners and, more recently, from internet-based scanning of media reports. The Public Health Agency of Canada's Global Public Health Intelligence Network (GPHIN), an electronic tool used by WHO since 1997, has demonstrated the value of using internet news sites for reports of outbreaks and unusual disease events. Similar media-scanning systems have been recently developed in other countries.[34] Project Argus at Georgetown University complements the internet-scanning technology with 30–40 analysts who have native language skills and local knowledge to provide context to the reports. The human-based Program for Monitoring Emerging Diseases (ProMED) was established in 1994. Over 40 000 subscribed members in over 160 countries submit reports of disease events.[35] National and multinational public health institutions have established specialized units, modeled on WHO's Alert and Response Operations, for monitoring and verifying event-based reports, coming particularly from countries with weak surveillance and reporting systems. CDC, the European Centre for Disease Prevention and Control, and the French Institute for Public Health Surveillance are a few notable examples.

Global surveillance networks all operate within the framework of the International Health Regulations (IHR), which outline WHO's authority and Member States' obligations to develop surveillance capabilities, report and prevent the spread of disease threats. The revised IHR (2005) entered into force in 2007. Countries were required to complete an assessment of their core surveillance and response capacities within 2 years and then have 3 years to implement the required measures for compliance. The revised IHR are much broader in scope than the preceding regulations. The IHR define a Public Health Emergency of International Concern (PHEIC) as any extraordinary public health event (all hazards) that constitutes a public health risk to other countries through international spread, and potentially requires a coordinated international response. State parties to the IHR are required to notify WHO about events that may constitute a PHEIC, which includes mandatory reporting of four diseases (smallpox, SARS, wild-type poliovirus infections, and novel subtypes of influenza) and an assessment of all other threats using a prescribed algorithm. WHO makes the final assessment of whether an event is a PHEIC. Of the many events reported by countries to WHO since IHR implementation in June 2007, pandemic H1N1 influenza was the first PHEIC declared by the WHO Director General in May 2009.

Whereas the IHR provide the legal framework for global control of infectious diseases, WHO's Global Outbreak Alert and Response Network (GOARN) is the operational arm, i.e., the mechanism by which WHO's partners respond to outbreaks of international importance.[32] GOARN activities are described below.

EXAMPLES OF SPECIALIZED SURVEILLANCE AND RESPONSE NETWORKS

Global Disease Detection Program

CDC's Global Disease Detection (GDD) program, established in 2004, develops and strengthens global capacity to rapidly detect, accurately identify, and promptly contain emerging infectious disease and bioterrorist threats that occur internationally.[36] The central focus of the GDD program are eight Regional Centers in China, Egypt, Guatemala, India, Kazakhstan, Kenya, South Africa and Thailand that build national and regional surveillance and response capacity in support of WHO and IHR (2005) implementation. The Atlanta-based GDD Operations Center is a centralized unit that creates an environment for joining CDC program expertise and disease intelligence from a vast array of sources, and supports CDC response operations when international assistance is requested.

Global Influenza Surveillance Network

Established in 1952, this global network of more than 120 institutions in 99 countries monitors influenza activity and collects the viral isolates that determine the composition of the following year's influenza vaccines[37,38] (*Fig. 14.2*). The isolates are characterized by WHO Collaborating Centers in the United Kingdom, Japan, Australia, and the United States. In addition to guiding the annual composition of recommended vaccines, the network operates as an early warning system for the emergence of influenza variants and novel strains that could signal the emergence of an influenza pandemic.

Global Laboratory Network for Poliomyelitis Eradication

International disease eradication strategies include a strong surveillance component. To support the Global Polio Eradication Initiative, WHO established the Global Laboratory Network for Poliomyelitis Eradication,[39] which uses molecular techniques to determine whether wild-type polio is circulating in areas undergoing eradication efforts. Genomic sequencing capabilities and collaboration among network laboratories have allowed the tracking of virus strains within and among countries and the identification of the origin of viruses imported into polio-free countries.[40]

Global Foodborne Infections Network (formerly known as WHO Global Salm-Surv)

Started in 2000, WHO's Global Salm-Surv is a global network of laboratories and individuals involved in isolation, identification, and antimicrobial resistance testing of *Salmonella* and surveillance of salmonellosis.[41] The scope of the network has recently broadened to include other pathogens and has been renamed the Global Foodborne Infections Network (GFN). The goal is to enhance the capacity and quality of foodborne and enteric pathogen surveillance, serotyping, and antimicrobial resistance testing throughout the world. GFN includes an electronic discussion group; international training courses for microbiologists and epidemiologists working in human health, veterinary and food sciences; external quality assurance testing; and focused research projects on topics such as surveillance enhancement and burden of illness. Member institutions enter their top 15 *Salmonella* serotypes yearly in a web-based country databank that can be searched for serotype frequency nationally, regionally, or globally.

PulseNet International

PulseNet International is a worldwide network of regional and national laboratory networks that utilizes standardized genotyping methods to enhance surveillance and provide early warning of food- and waterborne disease outbreaks, emerging pathogens, and acts of bioterrorism.[42] PulseNet promotes laboratory investigations of foodborne outbreaks through culture confirmation, and laboratories participating in the network use standard laboratory molecular subtyping protocols for all major bacterial pathogens transmitted via food and water and for *Yersinia pestis*. Disease case clusters originating from common source outbreaks, which may otherwise not be detected, are identified by sharing and comparing pulse-gel electrophoresis patterns (PFGE) patterns between participating laboratories.

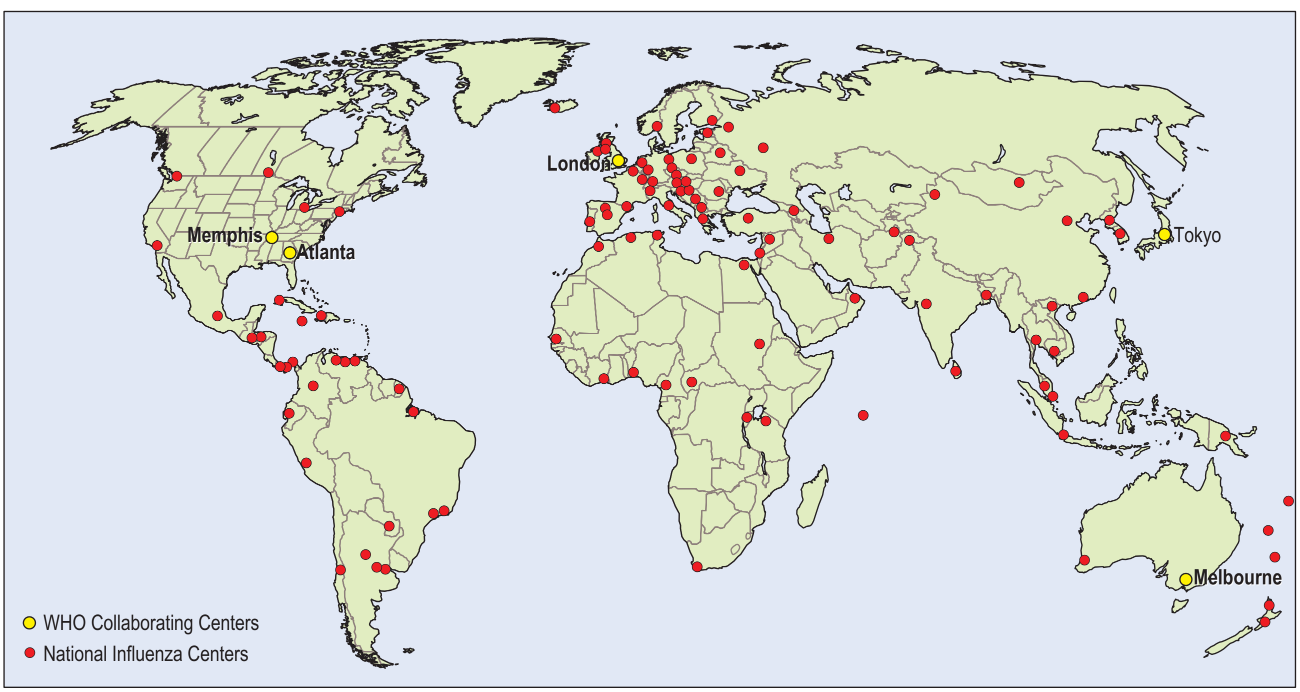

Figure 14.2 WHO Global Influenza Surveillance Network of five Collaborating Centers and 128 national influenza centers in 99 countries – September 24, 2009.

Drug Resistance Surveillance Projects

Surveillance of antimicrobial resistance is fundamental for understanding trends, developing treatment guidelines, and assessing the effectiveness of interventions. In 1994, WHO, the International Union against Tuberculosis and Lung Disease (IUATLD), and other partners launched the Global Project on Anti-Tuberculosis Drug Resistance Surveillance in response to growing concern about drug resistance and its impact on TB control. The purpose of this network of reference laboratories is to measure the prevalence of anti-TB drug resistance (single-drug resistant, multidrug-resistant, and extensively drug-resistant TB) in several countries using standard methods and to study the correlation between the level of drug resistance and treatment policies in those countries.[43] Monitoring antimalaria drug resistance has demonstrated increasing resistance that requires revision of treatment guidelines (see ***Fig. 96.4***). Recently, artemisinin resistance has been recognized in Cambodia.[44]

Global Outbreak Alert and Response Network

The Global Outbreak Alert and Response Network (GOARN) was launched in 2000 as a mechanism for combating international disease outbreaks, ensuring the rapid deployment of appropriate technical assistance to affected areas, and contributing to long-term epidemic preparedness and capacity building. GOARN electronically links more than 120 partner institutions and surveillance networks, which together possess the expertise, skills, and resources for rapid outbreak detection, verification, and response.[32] The coordinated response to the large Ebola hemorrhagic fever outbreak in Uganda in 2000 demonstrated the merit of the principles on which the network is based and functions.[18] The importance of GOARN was also evident in 2003, when WHO coordinated the unprecedented global response to SARS. Through GOARN, WHO assembled the international public health, clinical, and research communities to rapidly identify and characterize the causative agent and to contain the spread of this new infectious agent, providing a new standard for future responses to global microbial threats.[4]

THE CRITICAL ROLE OF THE LABORATORY

Microbiology laboratories play a critical role in surveillance for emerging infectious diseases and bioterrorism threats by identifying the microbial cause of disease syndromes, detecting and reporting new or unusual pathogens, and assessing antimicrobial resistance.[45,46] To carry out this role, laboratories require well-equipped, safe, and secure facilities, adequate human and financial resources, access to needed reagents, and robust quality control.

Accurate etiologic diagnosis is dependent on standardization of and scrupulous attention to a series of essential procedures. These include the collection and transport of appropriate clinical specimens, careful handling, accurate and complete labeling, and access to relevant clinical information to guide the testing process. Laboratorians also benefit from knowledge of the local epidemiologic situation. The chain of events is completed when the laboratory provides results to the medical staff to guide clinical management of the patient and to epidemiologists for cluster and trend analysis, monitoring, and response. Specimen collection requires an understanding of the samples needed (e.g., whole blood, serum, cerebrospinal fluid); proper containers for safe transport outside the clinical facility; labeling with information on the source and the time of collection relative to clinical status; proper packaging for shipping; and compliance with regulations for transport. The laboratory to which the specimens are being sent should be notified in advance to facilitate assistance with customs clearance and transport.

The critical needs of the laboratory center around three basic resources: equipment and supplies to safely conduct the required tests, reagents to test for the pathogens of interest, and trained staff to perform the testing. High-quality diagnostic reagents with positive and negative controls are critical, especially for viral diseases or locally unfamiliar diseases. For some agents, such as influenza, dengue, and hantaviruses, commercially available diagnostic kits can be used in settings with minimal laboratory facilities.

Proper biosafety containment and strict adherence to biosafety procedures are critical, as was demonstrated by the recurrence of SARS-CoV infections in Singapore, Taiwan, and China in late 2003/early 2004 due to lapses in laboratory containment.[47–49] Most organisms are classified in one of four biosafety levels (BSL), depending on the seriousness of the disease, their transmissibility, and the availability of effective treatment or vaccines.[50] BSL 3 and 4 are required for handling the most dangerous pathogens and require highly specialized facilities and potentially expensive physical plant requirements.

Field laboratories can be key to the rapid containment of outbreaks of emerging infectious diseases. This was shown in the 2000–2001 outbreak of Ebola hemorrhagic fever in Uganda, when testing at a field laboratory was linked with additional testing at CDC and other reference centers.[18,51]

Pathology laboratories and pathologists have also been critical to identifying the causal agents, describing the pathogenetic processes,[52] and guiding the early phases of the epidemiologic investigations of several recently described diseases, including hantavirus pulmonary syndrome,[53] new variant Creutzfeldt–Jakob disease,[54] SARS,[55] and Lujo virus, a newly recognized hemorrhagic fever-associated arenavirus in southern Africa.[56] Clinicopathologic studies have also helped in understanding diseases such as West Nile virus encephalomyelitis.[57] Immunologic and molecular methods, including immunohistochemistry, *in situ* hybridization, and polymerase chain reaction, have revolutionized the diagnosis and understanding of emerging infectious diseases, showing the importance of pathologists and medical examiners in surveillance.[52]

COMMUNICATIONS

Finally, rapid reliable exchange and dissemination of information on disease incidence and distribution in real time are critical and depend on formal and informal networks. The 2003 global SARS epidemic showed how laboratory scientists, clinicians, and public health experts, aided by electronic communications, rapidly generated the scientific basis for public health action. A "virtual" international network of laboratories, linked by a secure website and daily teleconferences, identified the causative agent and rapidly developed diagnostic tests.

Recently developed and enhanced technologies have helped create web-based public health tools for disease reporting and emergency communications. The US CDC communicates breaking surveillance information to public health officials through two electronic networks: the Epidemic Information Exchange (Epi-X), a secure mechanism for sharing health surveillance information on outbreaks and other unusual events, and the Health Alert Network (HAN), which links local, state, and federal health agencies and provides an electronic platform for emergency alerts and long distance training. Similarly the Early Warning and Response System tracks communicable diseases in Europe.[58] Globally, WHO shares information through Disease Outbreak News on the WHO website, and the *Weekly Epidemiological Record*.

It is also key (and a required core capacity in the IHR) to communicate about risk. Outbreaks of novel or reemerging infectious disease involve scientific uncertainties and high levels of public concern that health officials will be challenged to address. Since the 2001 anthrax attacks and the 2003 global SARS outbreaks, CDC and WHO have been actively involved in efforts to incorporate risk communication into public health practice, as demonstrated during the H1N1 influenza pandemic.

CONCLUSIONS

Future challenges posed by infectious agents are difficult to predict but certainly include the emergence of additional zoonotic agents that cross the species barrier to humans; the emergence of new bacterial strains that are more virulent or resistant to antibiotics; the possible deliberate release of pathogenic microbes by terrorists; the emergence of novel influenza viruses; the likelihood of increased spread of arbovirus infections, particularly dengue, West Nile and chikungunya and yellow fever viruses; and further outbreaks of cholera and foodborne diseases. The best defense against these mobile and resilient pathogens is timely and reliable infectious disease intelligence obtained through global public health surveillance.[32] The international community has made important strides in developing networks for detecting and reporting infectious disease events and enhancing capacity for clinical and laboratory surveillance. Continued commitment and support are needed to optimize these mechanisms to improve the timely detection of unusual disease events, strengthen the ability to share disease intelligence, and inform prevention and containment efforts.

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