

SECTION ONE

# **Introduction and Program-Area Surveillance Systems**



## 1

## Infectious disease surveillance: a cornerstone for prevention and control

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*In view of the galloping pace of globalization that is transforming the world into a global village, close international co-operation is essential in the detection, prevention, and control of communicable diseases.*

Leung Pak-yin, Centre for Health Protection,  
Hong Kong [1]

### Introduction

Throughout human history, infectious diseases have been a major force—constantly changing in form as new human behaviors pose new risks, old pathogens adapt, and novel pathogens emerge. The widespread availability of vaccines and antibiotics led to a mistaken confidence that infectious diseases had been conquered, as expressed by some United States (US) public health leaders in the late 1960s [2]. In the following decades, this optimism was replaced by a realization of the enormity of infectious disease challenges. New pathogens, including human immunodeficiency virus, have erupted while known pathogens, including drug-resistant tuberculosis and malaria, continue to cause major morbidity and mortality. Globally, infectious diseases are the leading cause of morbidity and the second leading cause of death [2].

The economic consequences associated with infectious diseases are enormous. Even in a small

country like England with a population of approximately 50 million persons, the direct cost of treating infectious diseases was estimated to be approximately £6 billion (US\$11.5 billion) per year [3]. Disease epidemics can undermine national and even global economic stability. The economic ramifications of the 2003 outbreak of severe acute respiratory syndrome (SARS) were experienced not only in Asian countries, but also globally. Direct and indirect economic costs of SARS have been estimated at US\$80 billion [4].

We will demonstrate in this chapter and throughout this book that to confront threats of endemic and emerging pathogens, systematic disease tracking is essential to inform disease prevention and control programs. The successful eradication of smallpox in the twentieth century (see Part 1 of Chapter 39, *The use of surveillance in the eradication of smallpox and poliomyelitis*) is a dramatic example of the central role played by surveillance in guiding disease control (Figure 1.1). Many other important, ongoing achievements in surveillance will be illustrated in this chapter. We will introduce the basic principles of infectious disease surveillance and present a glimpse into the vast array of innovative surveillance systems currently in place. To reinforce key concepts, examples will be chosen from real-life surveillance systems with reference to further details provided in subsequent chapters of this book.

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Fig 1.1 A child receiving smallpox vaccine. Surveillance data played a key role in smallpox eradication efforts by guiding vaccination campaigns.

### Definition and scope of infectious disease surveillance

General principles of public health surveillance are used in programs to prevent and control infectious disease, chronic disease, and injury, and to insure occupational health. In this book we focus on infectious disease surveillance, primarily as communicable pathogens relate to human health but also with attention to pathogens in the closely interrelated animal realm and environment. The infectious diseases surveillance activities described in this book are primarily carried out by public health authorities or infection control entities in healthcare institutions; however, modern infectious disease surveillance requires collaboration with partners in a variety of fields, including wildlife biology, veterinary medicine, law, and information technology (IT).

The conduct of surveillance can be conceived as a “three-legged stool” consisting of three main integrated activities: (a) systematic collection of pertinent data (e.g., case reports of a specific disease); (b) analyses of these data (e.g., assessing trends in disease occurrences); and (c) timely dissemination of results to guide interventions (e.g., reports to public health teams implementing prevention programs or

to clinicians to guide empiric disease management). The three surveillance “legs” are contained both in the original 1969 *International Health Regulations* and the most recent definition of surveillance as is articulated in the 2005 *International Health Regulations* (IHR 2005) [5]. IHR 2005 defines surveillance as “the systematic ongoing collection, collation and analysis of data for public health purposes and the timely dissemination of public health information for assessment and public health response as necessary.” These components are considered central to every public health surveillance system and will be revisited in this book as they pertain to specific programs.

Besides the World Health Organization (WHO), local, regional, and national agencies have embraced surveillance as a means to characterize and address endemic and emerging infectious disease threats. Although many of the examples covered in this book are from North America and western Europe, infectious disease surveillance is conducted worldwide, albeit in varying degrees and forms.

### What happens in the absence of infectious disease surveillance?

In considering the values of surveillance, it is instructive to ask, “What happens to public health in the absence of surveillance?” Where disease tracking is compromised, as occurs during protracted armed conflicts, previous progress made in disease control efforts can be reversed. For example, Somalia is one country where ongoing conflict has weakened the surveillance infrastructure necessary to identify and interrupt polio virus transmission [6]. Special investigations identified an outbreak of polio in Somalia that, between 2005–2006, resulted in an estimated 217 cases ([www.emro.who.int/polio/](http://www.emro.who.int/polio/)). The resurgence of polio in one country threatens eradication efforts in neighboring countries.

Lack of surveillance and control programs contribute to resurgence of diseases like human African trypanosomiasis in the Democratic Republic of Congo in the 1990s [7]. Gains made earlier in the century were lost during war and socioeconomic deterioration. By the time public health

teams were re-mobilized in 1993–1994, the incidence of trypanosomiasis was found to be 34,400, with neglected areas reporting the highest rates of the century. Impromptu surveillance and disease control measures can be expected to be much more difficult to implement in these and other countries that have suffered long-standing waves of violence and breakdown of the public sector infrastructure. Chapter 20 (*Communicable disease surveillance in complex emergencies*) offers practical considerations for conducting surveillance in complex emergency situations characterized by war or civil strife affecting large civilian populations. Examples are drawn from experiences in Albania, Basrah (Iraq), and the Greater Darfur region (Sudan).

Inadequate surveillance and consequent “blindness” to the health status of the population has contributed to the uncontrolled global spread of the human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), one of the worst pandemics in human history. Without accurate surveillance data to understand the true health status of their populations and to guide the use of limited public health resources, leaders can be grossly misinformed and, as in the case of HIV/AIDS, lose opportunities for early prevention and control before the virus becomes entrenched. Stigmatization,

discrimination, and marginalization—all fueled by ignorance—have contributed simultaneously to the denial and, paradoxically, to the explosion of the pandemic. As shown in Figure 1.2, in the 25 years since the first recognition of AIDS in the US, it is estimated that 65 million persons have been infected with HIV and more than 25 million have died of AIDS [8].

Complacency and diversion of resources have hindered maintenance of surveillance systems that are sensitive enough to detect smoldering epidemics. In the US during the mid-1980s, lack of support for tuberculosis surveillance and control is thought to have contributed to the subsequent multi-drug resistant tuberculosis outbreak which emerged in several geographic areas and resulted in more than \$700 million in direct costs for tuberculosis treatment in 1991 alone [9]. (Also see Chapter 12, *Surveillance for tuberculosis in Europe*.) Deterioration of public health infrastructure, including capacity to detect diseases, is thought to have contributed to the reemergence of epidemic diphtheria in the Russian Federation in 1990 and its spread to all Newly Independent States and Baltic States by the end of 1994 [10]. In a statement that specifically addressed the resurgence of vector-borne diseases in Europe (but also applies to other infectious

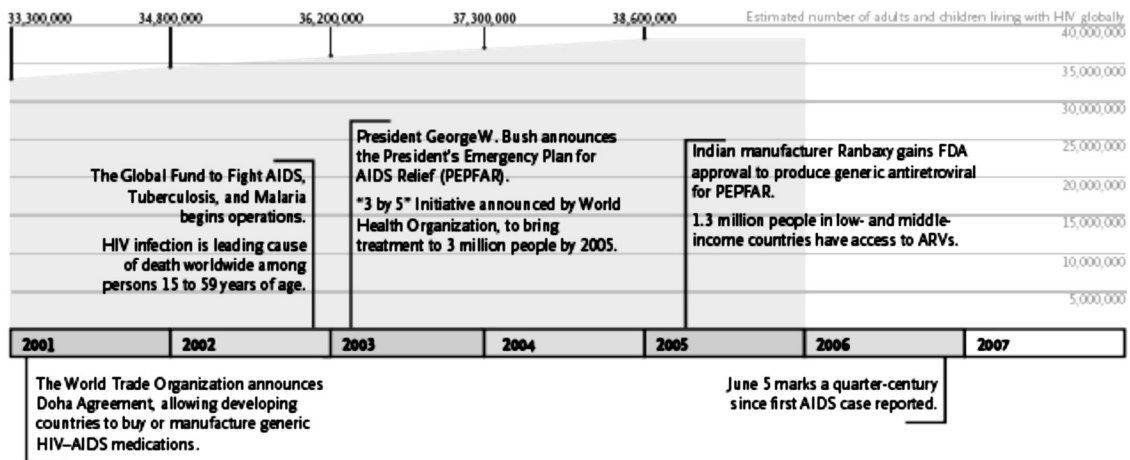


Fig 1.2 The Global HIV/AIDS Epidemic. For expanded timeline, see source: The Henry J. Kaiser Family Foundation, www.kff.org. Used with permission from the Henry J. Kaiser Family Foundation, Menlo Park, California [8].

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diseases), WHO stated in 2004, “In the absence of major and dramatic outbreaks, health authorities often fail to allocate adequate funding for the surveillance and control of this group of diseases” [11].

In disease eradication programs, robust surveillance systems are necessary to detect every case. However, with low levels of disease, it is hard to convince decision makers to allocate sufficient resources for surveillance and a risk of undetected relapse remains. As a result of an ambitious plan to eradicate malaria in the mid-1950s, some countries (e.g., India) had sharp reductions in the number of cases followed by, after efforts ceased, increases to substantial levels [12].

The desire of societies to control the spread of highly contagious and virulent infectious pathogens (e.g., pandemic strains of influenza virus) may allow acceptance of quarantine by public health authorities even at the expense of individual liberty. However, without surveillance data, public health officials will have difficulties designing rational isolation and quarantine strategies and can expect to encounter legal obstacles and public disapproval. Chapter 35 (*Legal considerations in surveillance, isolation, and quarantine*) underscores the need to support isolation and quarantine decisions with sound medical and epidemiologic evidence.

### The value of surveillance

Even with available surveillance data, what can public health programs realistically accomplish in terms of disease prevention and control? Merely collecting disease data for surveillance has little impact. However, successful surveillance programs also analyze and disseminate data to inform prevention and control activities. Specific programs, provided as examples here and further detailed later in this book, clearly illustrate the power of appropriately designed and utilized surveillance data.

#### Guide seasonal vaccine formulation

The WHO Global Influenza Surveillance Network, a network of 4 centers and 116 institutions in 87

countries, conducts annual surveillance for new strains of influenza (see Chapter 19, *Seasonal and pandemic influenza surveillance*). The results form the basis for WHO recommendations on the composition of influenza vaccine for the Northern and Southern hemispheres each year [13]. Use of surveillance data to guide production of influenza vaccine is critical because the vaccine is most effective when most antigenically similar to circulating viruses [14].

#### Guide vaccination strategies

Characterization of risk factors for bacterial infections such as invasive pneumococcal and meningococcal disease and data on circulating serotypes guide the development of vaccination recommendations. For example, in the US, data from active, population-based surveillance was used by public health advisory committees on immunization to help formulate the guidelines for vaccination of young children with a newly developed pneumococcal conjugate vaccine [15] and to recommend routine vaccination of incoming college students with meningococcal vaccine [16]. Further details are presented in Part 1 of Chapter 18 (*Surveillance for vaccine preventable diseases*).

#### Assess vaccine safety

Success of vaccination recommendations depends on their acceptance by the public and healthcare providers; an acceptable vaccine risk–benefit ratio is important in gaining this confidence. The establishment of surveillance for vaccine-associated adverse events has enabled ongoing assessment of vaccine safety. Exemplified by the US Vaccine Adverse Event Reporting System and the Yellow Card program used in the United Kingdom (UK) and other countries, this type of surveillance is important for detecting problems with vaccines (e.g., intussusception related to rotavirus vaccine) and, when supporting surveillance evidence exists, in promotion of vaccines with good safety records (see Part 2 of Chapter 18, *Vaccine adverse event reporting system*).

### Guide clinical management in the face of evolving antimicrobial resistance

Surveillance for antimicrobial-resistant organisms can guide clinical management for these infections, as well as increase awareness of the consequences of antibiotic overuse. For example, surveillance for community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) in the US has demonstrated that CA-MRSA has become a common and serious problem and that the infecting strains are often resistant to prescribed antimicrobial agents [17]. Chapter 4 (*Surveillance for antimicrobial-resistant Streptococcus pneumoniae*) and Chapter 14 (*Surveillance for community-associated methicillin-resistant Staphylococcus aureus*) discuss bacterial antibiotic resistance. Global surveillance for chloroquine-resistant and other types of resistant malaria greatly impacts recommendations for treatment and prophylaxis for persons traveling to specific countries [18]. *International Travel and Health*, a publication by WHO, is updated every year and can be downloaded from <http://www.who.int/ith/en/>. Health travel information is also available on the Centers for Disease Control and Prevention (CDC) Web site <http://www.cdc.gov/travel/>.

### Control emergence of antimicrobial-resistant organisms in domesticated animals

Widespread use of antimicrobial agents as growth promoters in animal husbandry is associated with increased resistance to antibiotics in bacteria isolated from animals and humans [19]. Surveillance for antimicrobial-resistant organisms in food animals is important to inform policies regarding use of antimicrobials outside human medicine. For example, the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) was established in 1995 to monitor antimicrobial resistance in bacteria from livestock, food, and humans, and to monitor use of antimicrobial agents [20]. Due to demonstration of rising antimicrobial resistance among bacteria isolated from food animals, Denmark banned use of certain antimicrobial agents as growth promoters in the 1990s (e.g., avoparcin, a glycopeptide similar to vancomycin, in 1995) [21]. For further discussions, see Chapter

### 7 (*Surveillance for antimicrobial-resistance among foodborne bacteria: the US approach*).

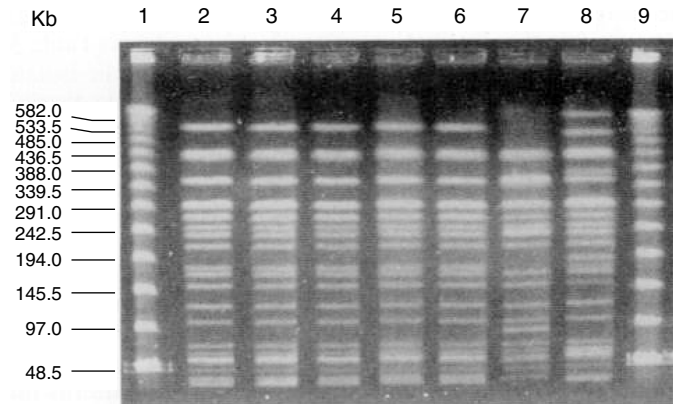
### Guide allocation of resources for disease prevention and treatment programs

Surveillance data are used to guide allocation of resources to control infectious diseases at various levels. For example, in the US, over \$2 billion from the Ryan White federal emergency financial assistance program are allocated to support HIV/AIDS care facilities based on the number of AIDS cases reported [22]. Annual estimates of the burden of HIV/AIDS in different countries by the United Nations Program on HIV/AIDS has stimulated creation of organizations (e.g., Global Fund to Fight AIDS, Tuberculosis and Malaria; and the Bill and Melinda Gates Foundation) focused on securing resources to expand public health programs in the countries most affected by HIV/AIDS [23,24].

### Identify outbreaks and guide disease control interventions

A major use of infectious disease surveillance data is to establish a baseline or reference point for detection of outbreaks requiring immediate investigation and intervention. Advancement in laboratory methods has enhanced usefulness of surveillance in outbreak detection by linking bacterial isolates obtained from geographically dispersed cases. For example, PulseNet is a national network of public health and food regulatory agency laboratories in the US that perform standardized molecular subtyping (or “fingerprinting”) of disease-causing foodborne bacteria by pulsed-field gel electrophoresis (PFGE) [25]. PFGE patterns of isolates are compared with other patterns in the database to identify possible outbreaks. In a large multistate *Escherichia coli* O157:H7 outbreak in 1993, PFGE was used to link cases with consumption of hamburgers from a restaurant chain (Figure 1.3) [26]. Public health action in Washington state prevented consumption of over 250,000 potentially contaminated hamburgers, preventing an estimated 800 cases [27]. See Chapter 5 (*Surveillance for foodborne diseases*) for discussions on detection and investigation of foodborne disease outbreaks.

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**Fig 1.3** PFGE of *E. coli* O157:H7 strains associated with a multistate outbreak. Lanes 1 and 9, molecular weight markers (lambda ladder); lanes 2–5, patient isolates from Washington, Idaho, Nevada, and California, respectively; lane 6, isolate from an incriminated lot of hamburger meat; lanes 7 and 8, isolates from lots of hamburger meat unrelated to the outbreak [26]. (Used with permission from American Society of Microbiology Journals Department.)

### Detect and respond to emerging infections

Surveillance is useful for detecting and controlling new or reemerging pathogens. The recent outbreak of SARS illustrates the role of surveillance in guiding response to an emerging global public health threat. First reported in Guangdong Province, China, in 2003, SARS resulted in 8098 probable cases with 774 deaths reported in 29 countries. Surveillance played a critical role in assessing the spread of the SARS epidemic and guiding quarantine recommendations and other control measures (see Chapter 39, Part 2, *SARS surveillance in Hong Kong and United States during the 2003 outbreak*).

### The spectrum of infectious disease surveillance and disease-reporting systems

Students and newcomers to the practice of public health may perceive surveillance to be synonymous with mandatory healthcare-provider-based disease reporting systems. Although disease reporting is important, there are other components of surveillance. We will outline core disease reporting systems as exemplified in the US and other countries, and then introduce the breadth of other types of innovative systems used to monitor and respond to infectious diseases.

#### Disease reporters

In most countries, mandatory disease reporting relies upon physicians or other healthcare providers

both to diagnose diseases designated to be of public health importance and to report these cases to public health authorities. However, other professionals are also obligated to report specific diseases. For example, laboratory directors are given responsibilities to report cases when laboratory tests are indicative of a reportable disease. In some countries, directors of schools, homes for the elderly, prisons, or other institutions are required to notify public health officials of any clusters of disease, such as two or more cases of suspected food poisoning.

Despite being legally mandated, diseases are grossly underreported [28]. There are essentially no penalties for failing to report cases of disease. Health-care providers and other reporters are often unaware of which diseases to report, they may not believe in the utility of surveillance, and the logistics of reporting cases can become unmanageable for busy clinicians. Creative means to motivate and support disease reporters is essential, but often overlooked. As one example, in the UK, a (modest) financial compensation is offered to persons who report diseases [29]. To promote reporting of HIV, Michigan Department of Community Health (US) maintains an active relationship with HIV care specialists through an e-mail group that provides up-to-date information on HIV and other infectious disease news (see Chapter 16, *Surveillance for HIV/AIDS in the United States*).

#### Diseases selected for surveillance

In most European countries, diseases considered to be of public health significance and warranting



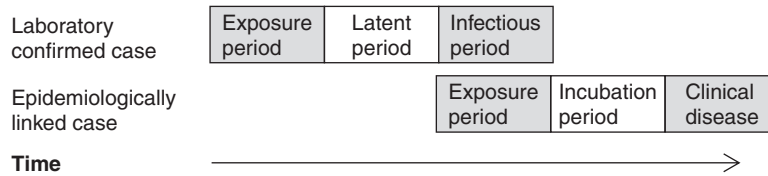


Fig 1.4 Guidance for defining an epidemiologically linked case prospectively. An epidemiological link is established when there is contact between two people involving a plausible mode of transmission at a time when (a) one of them is likely to be infectious and (b) the other has an

illness onset within the incubation period after this contact. At least one case in the chain of epidemiologically linked cases (which may involve many cases) must be laboratory confirmed [32]. (Used with permission of the Australian Government – Department of Health and Aging.)

systematic surveillance are selected at a national level. Provisions often do allow, however, for regional adaptation (see Chapter 6, *Supranational surveillance in the European Union*). For example, chikungunya was made a mandatory notifiable condition in mainland France and the overseas departments in the Caribbean, but not in the department La Réunion in the Indian Ocean, where a massive epidemic involving over 100,000 persons in 2006 overwhelmed the disease reporting structure. In the US, the authority to require disease reporting is decentralized—states, territories, and independent local health departments legislate lists of reportable diseases, and these vary by state. For example, coccidiomycosis is reportable only in areas in the southwestern US where the fungus is endemic.

#### Case definitions

Case definitions are specific clinical and/or laboratory criteria used to standardize surveillance data from different health jurisdictions. Before being counted as a case, a disease report is investigated to ensure that these criteria are met. The Council of State and Territorial Epidemiologists (CSTE), a professional society of public health epidemiologists, establishes and periodically revises case definitions that are used in infectious disease surveillance in the US [30] and are available on the CDC Web site <http://www.cdc.gov/epo/dphsi/casedef/>. Case classifications range from “confirmed” to “probable”, depending upon availability of supporting data.

For over 80% of nationally notifiable diseases in the US, positive laboratory test results are required for case confirmation, and many of the other dis-

eases require an epidemiologic link to a laboratory-confirmed case [31] (Guidance on identifying “epidemiologically linked” cases is provided in Figure 1.4 based on Australian case definitions [32]). Case definitions for some diseases such as tetanus rely primarily on clinical criteria (e.g., an acute onset of hypertonia and/or painful muscular contractions, usually of the muscles of the jaw and neck, and generalized muscle spasms without other apparent medical cause). Case definitions are subject to evolution—this may be necessary in the face of a rapidly changing epidemic of a new disease (see Part 2 of Chapter 39) or more slowly as in the case of HIV/AIDS (see Chapter 16). When case definitions are changed, data can be expected to be altered merely as an artifact of the new criteria [33].

The sensitivity and specificity of a case definition are influenced by the availability of good laboratory diagnostic assays to support clinical criteria, and by epidemiologic goals. In an outbreak or in other settings where confirmatory laboratory assays do not exist or are not practical, sensitive but less specific case definitions may be selected. For example, a gastrointestinal illness can be counted as a case of salmonellosis if epidemiologically linked to a laboratory-confirmed case of *Salmonella*. By contrast, when a single case has major public health implications, the case definition may be quite rigorous with strict laboratory criteria (e.g., for vancomycin-resistant *S. aureus* or the reemergence of SARS).

#### Data flow

Reporters phone, fax, mail, or electronically transmit case reports to local health jurisdictions that

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investigate, ensure that case definitions are met, and initiate interventions as needed. All states in the US voluntarily contribute surveillance data to the national system. As determined by CSTE, with input from CDC, a subset of locally reportable diseases is deemed “nationally notifiable” and this subset of cases are forwarded to the National Notifiable Disease Surveillance System at the CDC. In many other countries where the disease reporting authority is centralized at the national level, all cases confirmed at the local jurisdiction are forwarded to the national surveillance system.

## Dissemination of data

Surveillance data are compiled, analyzed, and presented at many levels. A prominent outlet in the US is the *Morbidity and Mortality Weekly Report*, where Surveillance Summaries on notifiable diseases are published on a freely accessible Web site, <http://www.cdc.gov/mmwr/>, and in printed copies that are mailed to subscribers. In the UK, surveillance data are published regularly in the *Communicable Disease Report Weekly*, available on the Health Protection Agency Web site <http://www.hpa.org.uk/cdr/default.htm> and by e-mail subscription. States, territories, and local health departments in the US have a variety of somewhat uneven methods to share surveillance data—use of the Web to support this data dissemination function is discussed in Chapter 21 (*Use of the World Wide Web to enhance infectious disease surveillance*). Of critical importance is sharing of information about infectious disease with the public. Chapter 32 (*Communication of information about surveillance*) covers this topic in two articles: Part 1 (*Media communication of surveillance information*) illustrates how the media conveys information and Part 2 (*Case study—a healthy response to increases in syphilis in San Francisco*) describes a public awareness campaign.

## Internationally notifiable diseases—International Health Regulations

Public health agencies of most countries operate fairly independently. However, infectious pathogens do not respect country borders, and therefore some disease outbreaks are not solely

the concern of the “index” country—intensified global public health response may become essential. IHR, as originally articulated by the World Health Assembly in 1969, has required countries to report cases of Yellow fever, plague, and cholera to the WHO. However, a 2005 revision broadens the scope of IHR to include not only an expanded list of known pathogens, but also as of yet undefined new or reemerging diseases which can spread rapidly with enormous health impact. International emergencies caused by noninfectious diseases are also addressed.

In the interests of the global community, the 2005 IHR addresses the need for an objective assessment of whether an event constitutes a public health emergency of international concern. As specified in the legal framework of the new regulations, WHO, with its extensive communications network, can rapidly assess information. Once it has determined that a particular event constitutes a public health emergency of international concern, IHR stipulates that WHO will make a “real-time” response to the emergency and recommend measures for implementation by the affected state as well as by other states. Official assessments from WHO, as an internationally prominent and neutral public health authority, can avoid unnecessary, uncoordinated interference with international traffic and trade that has previously made some countries reluctant to report significant events. For further discussion, see Chapter 2 (*Infectious disease surveillance and International Health Regulations*).

**Additional examples of the spectrum of infectious disease surveillance programs**

Some of the limitations encountered by disease reporting systems, including burden on reporters and subsequent underreporting, lack of representativeness, and focus on human diseases, are addressed by complementary systems. The principal alternate systems are described below.

## Laboratory-based surveillance

Clinical microbiology and public health laboratories can be rich sources of information on pathogens causing disease within a population. Compared

to individual healthcare providers who are often spread across multiple clinics and acute and chronic care facilities, laboratories may be a relatively consolidated source of data on reportable diseases. Many surveillance strategies involve collaborations with laboratories for sharing of data and isolates. For example, utilizing advancing information technologies, public health organizations have worked with clinical laboratories to enable electronic, automated transfer of information on reportable diseases to public health agencies (see Chapter 25, *Electronic reporting in infectious disease surveillance*, which offers electronic reporting examples from Germany and US). For an example of automated laboratory reporting using an Internet-based system, see Chapter 22 (*Infectious Diseases Surveillance Information System (ISIS) in the Netherlands: development and implementation*).

#### International surveillance systems

Although most surveillance systems are maintained by public health agencies within a given country, cooperation between countries have supported surveillance on a supranational and global scale. The international mandates of the IHR, as they apply to a small subset of exceptional diseases, have been discussed. An example of collaborative laboratory-based European surveillance is the European Antimicrobial Resistance Surveillance System (EARSS), which monitors seven major bacterial pathogens from 800 public health laboratories serving over 1300 hospitals in 31 European countries. EARSS was used to characterize methicillin-resistant *S. aureus* (MRSA) in participating European countries: during 1999–2000, MRSA prevalence varied from <1% of *S. aureus* isolates in northern Europe to >40% in southern and western Europe [34]. Facilitated by WHO, Global Salm-Surv is an example of an even larger global collaborative surveillance system. Five years after initiation, laboratories in 142 countries are sharing data on over 1 million *Salmonella* isolates, including 100,000 isolates from animals [35]. The WHO Global Influenza Surveillance Network, a network between 87 countries, is another example and is further described in Chapter 19.

#### Active surveillance

A misnomer used in describing surveillance is the term “passive” as this suggests minimal effort on anyone’s part. Customarily, the intent of labeling some surveillance systems as “passive” and others as “active” is to distinguish the intensity of public health agency’s effort in finding and investigating cases. State-mandated disease reporting systems in the US, while obviously relying on healthcare-provider energies, generally involve minimal public health effort to solicit case reports and thus are described as “passive.” Underreporting is a major limitation of this type of surveillance data. It is also true that no surveillance system should be entirely “passive,” even from the point of view of the public health agency, as regular communication and feedback to healthcare providers are necessary.

By contrast, “active” surveillance involves intensive public health involvement to seek reports of all diagnosed cases of a subset of reportable diseases, at least within defined regions, and to obtain additional epidemiologic and clinical information that may be missing from standard case reports. In actual practice, the distinction between both active and passive surveillance is not always so clear. An example is “enhanced passive” surveillance in which providers are actively solicited to assist in the identification of cases for a short-term surveillance study. For detailed discussions on active, population-based surveillance, including the Active Bacterial Core surveillance (ABCs) in the US and the Emerging Infections Program Network in Thailand, see Chapter 3 (*Population-based active surveillance for emerging infectious diseases*).

The Foodborne Disease Surveillance Network (FoodNET) established by the US CDC in collaboration with the US Department of Agriculture and the US Food and Drug Administration, and participating US Emerging Infection Program sites, is an active, laboratory-based surveillance program for foodborne pathogens [36]. Typically, only a small fraction of foodborne illnesses are reported to public health authorities, and often they lack accurate epidemiologic information (e.g., specific attributed causes, outcomes). To overcome these limitations, FoodNET investigators contact participating laboratories regularly to comprehensively identify all laboratory-confirmed cases of

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*Salmonella*, *Shigella*, *Campylobacter*, *E. coli* O157, *Listeria monocytogenes*, *Yersinia enterocolitica*, *Vibrio*, *Cryptosporidium*, and *Cyclospora* among persons in the predefined catchment area. As part of FoodNET, dedicated resources are used to conduct epidemiologic investigations of these cases. Discussions on FoodNET's contribution to public health are presented in Chapter 5.

## Sentinel surveillance

The intensive public health resources required to conduct population-based active surveillance are often not readily available; as an alternative strategy, sentinel surveillance involves collection of data from only a "sentinel" or subset of a larger population. The strategy of focusing only on a small population subset can be conceived as a type of "sampling." However, to be able to generalize these data to larger populations, it is necessary to ensure that the sentinel population is representative and that the sentinel data are linked to denominator information on a predefined population under surveillance (see discussion in Chapter 15, *Surveillance for viral hepatitis in Europe*).

The Gonococcal Isolate Surveillance Project systematically monitors antimicrobial resistance among *Neisseria gonorrhoeae* isolates collected from 25 to 30 sentinel US cities—antimicrobial susceptibility testing is performed on the first 25 isolates per month from male patients with gonococcal urethritis. In some states, rising resistance documented by this surveillance system has contributed to recommendations that fluoroquinolones should not be used to treat gonococcal infections (see Chapter 17, *Surveillance for sexually transmitted diseases*).

In France, a network of primary care physicians report information, at weekly intervals, on a selected group of health events that are relatively common in general practice: influenza-like illness, acute gastroenteritis, measles, mumps, chicken pox, male urethritis, hepatitis A, B, and C. Data are extrapolated to regional and national levels. The system detects and describes the occurrence and progression of regional and national outbreaks (available at: <http://rhone.b3e.jussieu.fr/senti>).

Multiple "sentinel" surveillance methods have been used to estimate the prevalence of HIV in

Africa and other countries. A commonly used approach has been through routine HIV testing for women presenting for antenatal care. Although sentinel surveillance can be useful, unique features of the sampled population such as contraceptive use may prohibit generalization to other populations [37].

## Animal reservoir and vector surveillance

Because of the central role of wildlife, domestic animals, and vectors (e.g., ticks and mosquitoes), zoonotic diseases cannot be adequately understood and controlled by only monitoring the disease in human populations. With increasing recognition of the importance of zoonotic diseases, surveillance systems have been designed to monitor pathogens as they circulate in various human and nonhuman hosts. Brucellosis control in the US has been successful because of the focus on animal health as a way to protect human health—comprehensive animal testing, vaccination of breeding animals, and depopulation of affected herds (see Chapter 8, *Surveillance for zoonotic diseases*). Although still requiring refinement, a major goal of surveillance for West Nile virus in the US is to be able to efficiently utilize dead bird, horse, or mosquito surveillance data to predict areas where transmission to humans is most likely to occur and therefore where vector control and other prevention efforts should be targeted (see West Nile virus case study in Chapter 9, *Surveillance for vector-borne diseases*).

## Detection of pathogens in the environment

The identification of the fungus *Cryptococcus gattii* in British Columbia, Canada, illustrates the use of surveillance to detect and define an emerging pathogen intrinsically linked to the environment. This fungus was previously known only in tropical and subtropical climates, but the organism emerged around 1999 in Vancouver Island as a pathogen in humans and domestic and wild animals. Environmental sampling has identified the fungus on trees, in soil, in air samples, and in water (Plate 1.1), helping to define the evolving realm of this new pathogen [38].

#### Use of health services and administrative data for disease surveillance

Infectious disease surveillance systems have also incorporated administrative and vital statistics data already being collected for other purposes. For example, vital statistics data are a component of HIV/AIDS surveillance as data are linked to identify (at-risk) infants born to women with previously reported HIV infection (see Chapter 16). To bill for services, healthcare facilities in the US assign diagnosis codes (e.g., International Classification of Diseases, Tenth Revision (ICD-10)) to clinical care encounters—this is a potential data source for surveillance for a range of diseases (see Chapter 17). Hospital admission data can also complement routine surveillance data; in England, hospital admission data have been used to monitor end-stage liver disease where the underlying cause is chronic viral hepatitis (see Chapter 15). Monitoring of drug utilization and drug sales may be an indirect measure of disease activity. Pharmaceutical databases have been explored for a variety of syndromic surveillance systems. At the US CDC, where a supply of “orphan” drugs are housed for treatment of rare diseases, increased requests for pentamidine in the 1980s led to an investigation of a cluster of *Pneumocystis* pneumonia which, in turn, led to the first detection of AIDS in the world [39]. Hospital administrative data are also used to conduct surveillance for hospital-associated infections (see Chapter 13, *Surveillance for nosocomial infections*).

#### Use of media reports for disease surveillance

The availability and speed of information transmission over the Internet have allowed development of innovative electronic media-based surveillance systems. For example, the Global Public Health Intelligence Network (GPHIN) gathers, in seven languages on a real-time, 24/7 basis, electronic media reports of occurrence of diseases. Although the electronically gathered information requires further verification, GPHIN is used extensively as an early source of outbreak information by Health Canada, WHO, the US CDC, and others (see Chapter 23, *The Global Public Health Intelligence Network*).

#### Risk-factor surveillance

Although most surveillance systems focus on disease occurrences or circulation of pathogens causing disease, unique surveillance systems have focused on behaviors that pose risk for specific diseases. For example, the US National HIV Behavioral Surveillance system includes interviews of a sample of persons to assess the prevalence of sexual behaviors, drug use, and testing history for other sexually transmitted infections [40]. Data from this system examine the front end of the HIV/AIDS epidemic and may guide and assess prevention programs (see Chapter 29, *Analysis and interpretation of case-based HIV/AIDS surveillance data*). Similarly, Youth Risk Behavior Survey measures the prevalence of health-risk behaviors among adolescents through self-administered, school-based surveys. Reports of sex without condoms and sex associated with drug and alcohol use are among the data collected [41] (see Chapter 17).

#### Use of computer algorithms to conduct surveillance

A few surveillance systems have been developed that employ computer algorithms to screen electronic data sources for disease cases and apply automated statistical methods to assess data trends and changes in case activity. For example, a component of the Infectious Diseases Surveillance and Information System (ISIS) in the Netherlands runs automated algorithms on electronically-transmitted laboratory data to identify selected cases of public health interest (e.g., new positive *Neisseria gonorrhoea* test results). Automated time-series analyses process these and other surveillance data to detect variations from expected rates; statistically significant changes automatically generate and distribute alerts (see Chapter 22). Syndromic surveillance systems use automated data extraction and analyses methods to detect aberrations from expected levels of various syndromes (see Chapter 26, *Implementing syndromic surveillance systems in the climate of bioterrorism*, for further discussion). Chapter 23 describes use of automated algorithms to scan 20,000 electronic news media sources for early reports of outbreaks around the world. Although these systems exhibit the powerful capacity of technologies to automatically process enormous

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quantities of data, humans must still verify, investigate, and prioritize these reports. Research is needed to refine these automated data processing systems and capitalize on their strengths.

### **Surveillance collaborations with partners outside traditional human public health systems**

As illustrated by the broad variety of infectious disease surveillance systems, diverse sources of information can be utilized. The development of these systems relies upon new collaborations between human public health agencies and nontraditional partners. For example, domestic and wildlife animal health agencies have traditionally acted as separate entities apart from human health agencies. However, the increasing recognition of the importance of zoonotic diseases to human health has encouraged innovative collaborations. When West Nile virus emerged in the US, public health officials who customarily focused only on human diseases began forging collaborations with entomologists, veterinarians, and wildlife oversight agencies [42]. Human health agencies often do not have these diversely skilled personnel, but instead depend upon common goals and national agendas to facilitate collaborations.

In broad terms, surveillance requires consultations with legal partners to interpret laws as they relate to public health activities, for example, ensuring maintenance of patient confidentiality during collection of electronic data (see Chapter 35, Part 1, *Legal basis for infectious disease surveillance and control*). The need for review of public health surveillance practices from an ethicist's perspective is discussed in Chapter 34 (*Ethical considerations in infectious disease surveillance*). As described in Chapter 11 (*Surveillance for unexplained infectious disease related deaths*), medical examiners have the authority to investigate sudden, unattended, and unexplained deaths. Although the focus of these investigations has traditionally been on intentional or accidental deaths, public health agencies have collaborated with medical examiners to systematize specimen collection and diagnostic testing relevant for detection of reportable, emerging, or bioterrorism-related infec-

tious diseases. Chapter 10 (*Surveillance for agents of bioterrorism in the United States*) also discusses collaboration with regional poison control centers in monitoring suspicious reports.

Syndromic surveillance systems use a variety of nontraditional data sources (e.g., employee absenteeism data, emergency department admission diagnoses). This has led to collaborations with academic institutions, healthcare institutions, and private sector IT specialists. Chapter 26 discusses some of the potential challenges faced in these collaborations, particularly in the investigation of surveillance data collected outside of public health jurisdictions (e.g., information not related to reportable diseases).

Today's increasingly complex surveillance systems require advanced data analysis and data management support. To adjust for missing data, account for confounders through multivariate modeling, and formally assess trends and clusters that may necessitate input from individuals with advanced training in biostatistics. Chapter 27 (*Informatics and software applications for data analyses*) and Chapter 28 (*Analyses and interpretation of reportable infectious disease data*) provide background on common software applications and analytic methods used in surveillance. Chapter 29 introduces issues in analysis and interpretation of case-based HIV/AIDS surveillance data. Collaborations with IT specialists have become essential and, for example, have enabled practical use of the Internet, ranging from posting practical disease reporting and surveillance information on the Web to development of Web-based means for reporting (see Chapter 21). Close collaborations between IT experts, stakeholders, and end users are critical in all phases of system design and testing to ensure the viability of these potentially multimillion dollar projects.

In the US and elsewhere, surveillance is not a wholly government function. For example, at their own cost, private hospital laboratories transmit large amounts of reportable disease information to health departments. Chapter 38 (*Public-private partnerships in infectious disease surveillance*) details the expanding role of the private sector in surveillance. Another example of public-private partnership is the US Vaccine Adverse Events Reporting System. While federal public health agencies set programmatic objectives and

provide technical oversight, the for-profit Constella Group is contracted to support this surveillance system's data collection processes [43]. These types of "mixed model" partnerships may be able to harness private-sector energy and efficiency while remaining faithful to public health objectives.

### **Challenges and promises for the future of infectious disease surveillance**

Progress in development of surveillance systems supports advances in disease prevention and control. However, public health challenges in surveillance and disease control continue to be faced around the globe. Despite IHR (2005) mandates [44], not all countries are able to devote adequate resources to surveillance. Countries are attempting to balance using limited resources to develop disease control and prevention programs (including surveillance as one important component) with the need to support struggling healthcare systems in the treatment of diseases. It may seem that the more pressing priority is to try to address the needs of persons who are already suffering from disease, rather than diverting resources towards surveillance and disease prevention. This sentiment is most acutely felt when countries cannot, because of lack of sufficiently trained workforces, maximize the benefits of surveillance and constructively use surveillance data for long-term disease prevention and control.

The gap between data collection and effective use of data for disease control and prevention is among the most formidable challenges faced by surveillance programs. An unfortunate reality of public health surveillance is that substantial efforts are spent on collection of data while sufficient resources are often not expended on timely dissemination and constructive use of the information. If these data are not appropriately analyzed, disseminated, and applied, surveillance will be perceived as categorically ineffective. As William Foege, former director of the CDC once remarked, "The reason for collecting, analyzing, and disseminating information on a disease is to control that disease. Collection and analysis should not be allowed to consume resources if action does not follow" [45].

Public health officials need to be sufficiently trained to be able to leverage benefits of surveil-

lance. In many countries, workforce with adequate skills to carry out core surveillance activities including data collection, analysis, and use of data for disease prevention and control is limited (see Chapter 24, *National notifiable disease surveillance in Egypt*). While much of the practice of surveillance may be learned on the job as newly hired personnel begin careers in public health, selected epidemiology training programs (see Chapter 36, *Training in applied epidemiology and infectious disease surveillance: contributions of the Epidemic Intelligence Service*, and Chapter 37, *Surveillance training for Fogarty International Fellows from Eastern Europe and Central Asia*) have given special attention to surveillance. Through formal evaluations of in-use surveillance programs, EIS officers not only begin to understand real-life surveillance, but also bring fresh perspective to systems that may have become stagnant. In collaboration with many countries' Ministries of Health, the Field Epidemiology (and Laboratory) Training Program and Data for Decision Making program offer training around the world in applied epidemiology, including issues in surveillance (available on the CDC Web site at: <http://www.cdc.gov/descd/>). Practical training on actionable surveillance should also be an emphasis in schools of public health and other educational arenas.

Ongoing evaluations are repeatedly needed as a core component of living surveillance systems. Are components of a surveillance system operating as effectively as possible, and if not, what changes can be made? For an introduction to formal evaluation of surveillance, see Chapter 33 (*Evaluation of surveillance systems for early epidemic detection*). Surveillance systems face the challenges of chasing moving targets—as more is learned about the epidemiology of a disease, surveillance strategies must be adapted. Emerging pathogens add further complexities. Surveillance systems need to be regularly reviewed, refined, and reenergized.

On the promising frontiers of public health, technical advancements are assisting efforts to improve surveillance systems. Examples include sophisticated IT instruments mentioned previously. Molecular fingerprinting has the capacity to improve epidemiologic understanding of links between human cases, management of outbreaks, and links to animal reservoirs (see Chapter 30,

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*Use of molecular epidemiology in infectious disease surveillance*). In the future, geographic information systems may hold new promises (see Chapter 31, *Use of geographic information systems and remote sensing for infectious disease surveillance*) to analyze multiple layers of geographical, ecological, and climatic information to assist in prediction of zoonotic and other diseases linked with the environment. New tools to enhance infectious disease surveillance continue to be developed; how to optimize the use of both old and new surveillance tools to inform disease prevention and control remains both an ongoing challenge and an opportunity.

## References

- 1 Hong Kong Health Commitment Pledged in Sweden. Available from: <http://www.news-medical.net/?id=5119>. Accessed October 16, 2005.
- 2 Fauci AS. Infectious diseases: considerations for the 21st century. *Clin Infect Dis* 2001;32:675–85.
- 3 Health Protection Agency. Health protection in the 21st century. Available from: [http://www.hpa.org.uk/publications/2005/burden\\_disease/default.htm](http://www.hpa.org.uk/publications/2005/burden_disease/default.htm). Accessed November 1, 2006.
- 4 Knobler S, Mahmoud A, Lemon S, Mack, A, Sivitz L and Oberholtzer K (eds). Workshop summary. In: *Learning from SARS: Preparing for the Next Disease Outbreak*. Washington, DC: National Academies Press; 2004:11.
- 5 World Health Assembly. Revision of the International Health Regulations, WHA58.3. 2005. Available from: [http://www.who.int/gb/ebwha/pdf\\_files/WHA58-REC1/english/Resolutions.pdf](http://www.who.int/gb/ebwha/pdf_files/WHA58-REC1/english/Resolutions.pdf). Accessed on October 27, 2006.
- 6 Centers for Disease Control and Prevention. Progress toward poliomyelitis eradication—Eastern Mediterranean Region, January 2000–September 2001. *Morb Mortal Wkly Rep* 2001;50:1113–6.
- 7 Ekwanzala M, Pepin J, Khonde N, Molisho S, Bruneel H, De Wals P. In the heart of darkness: sleeping sickness in Zaire. *Lancet* November 23, 1996;348:1427–30.
- 8 Merson MH. The HIV-AIDS pandemic at 25—the global response. *N Engl J Med* 2006;354:2414–7.
- 9 Berkelman RL, Bryan RT, Osterholm MT, LeDuc JW, Hughes JM. Infectious disease surveillance: a crumbling foundation. *Science* 1994;264:368–70.
- 10 Dittmann S, Wharton M, Vitek C, *et al.* Successful control of epidemic diphtheria in the states of the Former Union of Soviet Socialist Republics: lessons learned. *J Infect Dis* 2000;181(suppl 1):S10–22.
- 11 World Health Organization. The vector-borne human infections of Europe: their distribution and burden on public health. Available from: <http://www.euro.who.int/document/E82481.pdf>. Accessed November 7, 2006.
- 12 Sharma VP, Mehrotra KN. Malaria resurgence in India: a critical study. *Soc Sci Med* 1986;22:835–45.
- 13 World Health Assembly. Global influenza surveillance. Available from: <http://www.who.int/csr/disease/influenza/influenzane트워크/en/index.html>. Accessed November 3, 2006.
- 14 Centers for Disease Control and Prevention. Efficacy and Effectiveness of Inactivated Influenza Vaccine. Available from: <http://www.cdc.gov/flu/professionals/vaccination/efficacy.htm>. Accessed November 9, 2006.
- 15 Van Beneden CA, Whitney CG, Levine OS, for the Centers for Disease Control and Prevention. Preventing pneumococcal disease among infants and young children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2000;49(RR-9):1–38.
- 16 Bilukha OO, Rosenstein N; National Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC). Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2005;54(RR-7):1–38.
- 17 Fridkin SK, Hageman JC, Morrison M, *et al.*, Active Bacterial Core Surveillance Program of the Emerging Infections Program Network. Methicillin-resistant *Staphylococcus aureus* disease in three communities. *N Engl J Med* 2005;352:1436–44.
- 18 World Health Organization. Monitoring antimalarial drug resistance. Report of a WHO consultation, Geneva, Switzerland, December 3–5, 2001.
- 19 Fey PD, Safranek TJ, Rupp ME, *et al.* Ceftriaxone-resistant salmonella infection acquired by a child from cattle. *N Engl J Med* 2000;342:1242–9.
- 20 Danish Integrated Antimicrobial Resistance Monitoring and Research Programme. Monitoring antimicrobial resistance in Denmark. *Int J Antimicrob Agents* 2000;14:271–4.
- 21 Aarestrup FM, Seyfarth AM, Emborg HD, Pedersen K, Hendriksen RS, Bager F. Effect of abolishment of the use of antimicrobial agents for growth promotion on occurrence of antimicrobial resistance in fecal enterococci from food animals in Denmark. *Antimicrob Agents Chemother* 2001;45:2054–9.
- 22 Mokotoff ED, Glynn MK. Surveillance for HIV/AIDS in the United States. In: M'ikanatha NM, Lynfield R, Van Beneden CA, De Valk H (eds), *Infectious Disease Surveillance*. London: Blackwell; 2007:201–11.
- 23 United Nations Programs on HIV/AIDS. Uniting the World Against AIDS. Available from: <http://www.unaids>.



- org/en/HIV\_data/default.asp. Accessed November 7, 2006.
- 24 Bill and Melinda Gates Foundation. Available from: <http://www.gatesfoundation.org/default.htm>. Accessed December 26, 2006.
  - 25 Centers for Disease Control and Prevention. PulseNet. Available from: <http://www.cdc.gov/pulsenet/index.htm>. Accessed November 9, 2006.
  - 26 Barrett TJ, Lior H, Green JH, *et al.* Laboratory investigation of a multistate food-borne outbreak of *Escherichia coli* O157:H7 by using pulsed-field gel electrophoresis and phage typing. *J Clin Microbiol* 1994;32:3013–17.
  - 27 Bell BP, Goldoft M, Griffin PM, *et al.* A multistate outbreak of *Escherichia coli* O157:H7-associated bloody diarrhea and hemolytic uremic syndrome from hamburgers: the Washington experience. *JAMA* 1994;272:1349–53.
  - 28 Doyle TJ, Glynn MK, Groseclose SL. Completeness of notifiable infectious disease reporting in the United States: an analytical literature review. *Am J Epidemiol* 2002;155:866–74.
  - 29 Bannister BA, Begg NT, Gillespie SH. *Infectious Diseases*. London: Blackwell Science; 1996:455.
  - 30 Centers for Disease Control and Prevention. Case definitions for infectious conditions under public health surveillance. *MMWR Recomm Rep* 1997;46(RR-10):1–55.
  - 31 Smith PF, Birkhead GS. Electronic clinical laboratory reporting for public health surveillance. In: M'ikanatha NM, Lynfield R, Van Beneden CA, De Valk H (eds), *Infectious Disease Surveillance*. London: Blackwell; 2007:Pt 2, 339–48.
  - 32 Commonwealth of Australia. Australian notifiable diseases case definitions. Available from: <http://www.health.gov.au/internet/wcms/publishing.nsf/Content/cda-surveil-ndss-casedefs-epilink.htm#epi>. Accessed November 27, 2006.
  - 33 Schwarcz SK, Hsu LC, Parisi MK, Katz MH. The impact of the 1993 AIDS case definition on the completeness and timeliness of AIDS surveillance. *AIDS* 1999;13:1109–14.
  - 34 Tiemersma EW, Bronzwaer SL, Lyytikäinen O, *et al.* European Antimicrobial Resistance Surveillance System Participants. Methicillin-resistant *Staphylococcus aureus* in Europe, 1999–2002. *Emerg Infect Dis* 2004;10:1627–34.
  - 35 World Health Organization. Global Salm-Surv. Available from: <http://www.who.int/salmsurv/en/> Accessed November 5, 2006.
  - 36 Centers for Disease Control and Prevention. FoodNet Surveillance. Available from: <http://www.cdc.gov/foodnet/surveillance.htm>. Accessed November 5, 2006.
  - 37 Gregson S, Terceira N, Kakowa M, *et al.* Study of bias in antenatal clinic HIV-1 surveillance data in a high contraceptive prevalence population in sub-Saharan Africa. *AIDS* 2002;16:643–52.
  - 38 MacDougall L, Fyfe M. Emergence of *Cryptococcus gattii* in a novel environment provides clues to its incubation period. *J Clin Microbiol* 2006;44:1851–2.
  - 39 Centers for Disease Control and Prevention (CDC). Pneumocystis pneumonia—Los Angeles. *MMWR Morb Mortal Wkly Rep* 1996;45:729–33.
  - 40 Centers for Disease Control and Prevention. Human immunodeficiency virus (HIV) risk, prevention, and testing behaviors—United States, National HIV Behavioral Surveillance System: men who have sex with men, November 2003–April 2005. *MMWR Morb Mortal Wkly Rep* 2006;55(SS-6):1–16.
  - 41 CDC. Youth Risk Behavior Surveillance—United States, 2001. *MMWR Morb Mortal Wkly Rep* 2002; 51(SS04):1–64.
  - 42 Fine A, Layton M. Lessons from the West Nile viral encephalitis outbreak in New York City, 1999: implications for bioterrorism preparedness. *Clin Infect Dis* 2001;32:277–82.
  - 43 Constella Group. Constella Health Sciences Rewins CDC and FDA's \$21 Million Vaccine Adverse Event Reporting System Contract. Available from: [http://www.constellagroup.com/news/news\\_releases/2004/010404.shtml](http://www.constellagroup.com/news/news_releases/2004/010404.shtml). Accessed November 27, 2006.
  - 44 Hardiman BJM, González-Martin F, Rodier G. Infectious disease surveillance and the International Health Regulations. In: M'ikanatha NM, Lynfield R, Van Beneden CA, De Valk H (eds), *Infectious Disease Surveillance*. London: Blackwell; 2007:18–31.
  - 45 Foege WH, Hogan RC, Newton LH. Surveillance projects for selected diseases. *Int J Epidemiol* 1976;5:29–37.