Surveillance and Seroepidemiology

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Ruth Jiles, Monina Klevens, and Elizabeth Hughes

1 Introduction

The term *surveillance* was employed for years in the restrictive sense to imply follow-up of exposed persons to determine whether disease developed within the limits of the incubation period. The dictionary definition of surveillance is "close observation, especially over a spy or criminal" [67]. Surveillance, in the context of health, has been defined as the systematic collection of data pertaining to the occurrence of specific diseases, the analysis and interpretation of these data, and the dissemination of consolidated and processed information to contributors, programs, and other interested persons. The Centers for Disease Control and Prevention (CDC) has described surveillance as the collection of "health related data essential to the planning, implementation, and evaluation of public health practice, closely integrated with the timely dissemination of these data to those responsible for preventing and controlling disease and injury" [89].

Surveillance systems are developed and implemented for the ultimate purpose of preventing or controlling diseases. Historically, the principles of surveillance were well described and documented by Langmuir [57] and other officials of the US Public Health Service, CDC [6, 66], and by Raška [76, 77] for the World Health Organization (WHO) [108].

The techniques of surveillance and uses of surveillance data were applied first to infectious diseases and subsequently to occupational, environmental, and chronic diseases, as well as to injuries and emergency preparedness [6, 14]. *Healthy People*, the principal document of the US Department of Health and Human Services that outlines the health objectives for the United States, relies heavily on surveillance data to establish goals, baseline measures, and monitor progress towards achieving those goals [94]. The importance of surveillance and the need for improving surveillance techniques, both in developed and developing countries, have been well documented [68]. To improve data quality and timeliness of reporting, electronic transmission of surveillance data, mainly laboratory results, was initially implemented in the United States and France [39, 95]. Early challenges included standardization of case definitions and reporting methods among official sources. These issues were addressed in the US National Notifiable Disease Surveillance System through consensus and development of standard case definitions and reporting protocols.

This chapter discusses the background and elements of traditional surveillance, the concept and uses of serological and molecular epidemiology, and their application to the control of viral infections.

2 Surveillance

Traditionally, surveillance was based on the occurrence and reporting of a case of clinical disease or death. Currently, other life and infection-related events, such as births, hospitalization, risk behaviors and exposures, treatment, and healthcare system encounters, are also under surveillance.

2.1 Historical Background

A more detailed history of public health surveillance was published by Declich and Carter in 1994 [24] and summarized

R. Jiles, MS, MPH, PhD (✉)
Division of Viral Hepatitis, Department of Health and Human Services Centers for Disease Control and Prevention
Office of Infectious Diseases, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, 1600 Clifton Road, NE Mail Stop G-37, Atlanta, GA 30333, USA
e-mail: rxg0@cdc.gov

M. Klevens, DDS, MPH • E. Hughes, MS, DrPh
Division of Viral Hepatitis, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, 1600 Clifton Road, NE Mail Stop G-37, Atlanta, GA 30333, USA
e-mail: monina.klevens@cdc.hhs.gov;
elizabeth.hughes@cdc.hhs.gov

in an earlier version of this chapter [33]. Based on these accounts, various governmental actions to prevent spread of infections and diseases occurred during the seventeenth century. However, it is widely accepted that public health surveillance dates back to 1662, when John Graunt published the *Natural and Political Observations Made Upon the Bills of Mortality*. Graunt analyzed London's mortality data collected for the Bills of Mortality and was the first to count the number of deaths from specific causes (numerator), estimate the population (denominator), and use the information to determine death rates [41].

During the eighteenth century, some colonies in Rhode Island implemented various specific components of public health surveillance, requiring tavern keepers to report cases of "contagious" diseases such as smallpox, yellow fever, and cholera among their customers.

During the nineteenth century, several significant contributions were made in public health surveillance. Sir Edwin Chadwick, Secretary of the Poor Law Commission in England, used surveillance data to demonstrate that poverty and disease were associated and suggested improvement in the living conditions of the poor. In the United States, Lemuel Shattuck related living conditions to infant and maternal morbidity, mortality, and rates of death. He recommended collection of health data by such factors as age, gender, and occupation. William Farr, founder of a modern concept of surveillance, as the first Compiler of Abstracts for England and Wales, set up a system that not only tracked births and deaths, but also routinely recorded cause of death by occupation. Farr developed a nosology that is the basis for the International Classification of Diseases (ICD) (See http://www.cdc.gov/nchs/data/misc/classification_diseases2011.pdf).

Surveillance concepts and methodologies were developed in response to national needs for disease surveillance or in response to epidemics. Surveillance data were needed to define the magnitude of the problem and to inform policy/decision makers and others who were responsible for development, implementation, and/or evaluation of prevention and intervention programs and policies. Use of the term "surveillance" in the United States began in 1949 with the development of a modified program at the CDC called "Surveillance and Appraisal of Malaria." In 1951, the concept was applied to the residual smallpox cases in the United States.

On April 28, 1955, the Surgeon General of the United States directed the establishment of a "National Poliomyelitis Surveillance Program" in response to paralytic polio cases following the use of Salk vaccine (the "Cutter Incident"). Based on this program, established at the CDC, surveillance methods became an effective tool in following trends in the disease, in measuring the effectiveness of polio immunization programs, and in detecting suspected vaccine-associated cases. Likewise, other surveillance systems and units were developed in response to occurrence of other epidemics. WHO established regional, national, and international control programs with surveillance as an essential component of each type of control program. While European unification was anticipated, individual countries employed different approaches to surveillance; thus, there were concerns about comparability of data and coordination of activities [27]. The AIDS epidemic which began in the late 1970s and early 1980s forced many countries to establish new surveillance systems and improve existing ones.

While a set of legal and ethical principles of surveillance had been evolving gradually prior to the early 1980s, the pressing need for accurate information about HIV infection led to a broad array of new surveillance practices that have continued to test the balance between individual and community interests and responsibilities.

2.2 Types of Surveillance

Surveillance systems may be classified in a variety of ways: based on the method of reporting (passive or active), purpose of the system (Behavioral Risk Factor Surveillance System or BRFSS) [11], location (clinic based), or target population (Youth Risk Behavior Survey YRBS) [21].

The most common type of surveillance is passive. In passive surveillance the reporter, usually a physician or laboratory, regularly transmits a summary of all the cases of the specified disease or diseases observed to health authorities during the reporting period.

The US National Notifiable Disease Surveillance System (NNDSS) is an example of passive reporting [17]. States send case reports of nationally notifiable diseases to the CDC on a weekly basis. States determine which diseases are reportable within their jurisdiction and who (laboratory, physician, clinic, or some combination) initiates the report. State epidemiologists and CDC subject matter experts collaborate, through the Council of State and Territorial Epidemiologists (CSTE), to develop case definitions and define reportable data elements for reportable diseases. Generally, laboratories and/or physicians report cases to the local health departments, local health departments report cases to state health departments, and state health departments notify CDC of confirmed cases. Most laboratory reports and some physician reports are submitted electronically. However, reporting can be accomplished in print, by telephone, even using toll-free numbers or automatic recording devices available at all hours. Time and lack of resources greatly limit such a system to a small percentage of most reportable diseases, but as long as the system and requirements remain unchanged, the changes in incidence may reflect meaningful patterns of disease.

Active surveillance requires contacting the reporters at regular intervals and request for specific data on cases of

specified diseases. It permits more extensive data collection on epidemiologic features of certain diseases. CDC's Behavioral Risk Factor Surveillance System (BRFSS) is an active surveillance system [11]. States contact residents by telephone and administer a standardized questionnaire to eligible consenting adults aged 18 years or older to obtain information about a variety of chronic diseases and related risk behaviors. Relevant to viral infections, the BRFSS includes questions about receipt of influenza, shingles, and human papilloma virus vaccination. The BRFSS has also been used by CDC to provide state-specific estimates of HIV-related behaviors such as ever tested for HIV, where tested, and why tested. Some states conduct active surveillance for HIV/AIDS using other data sources.

For a few diseases, some special clinical feature of the disease may be used to estimate prevalence data. For example sudden severe acute lower respiratory illness may indicate hantavirus infection or jaundice may be evidence of hepatitis. In some instances, surveillance is based on laboratory data, as with the isolation of the agent or results of a serological test. In the case of viral hepatitis, the CDC/CSTE case definition includes both clinical features and laboratory test results. Most surveillance systems cover political jurisdictions (e.g., national, state, and county). However, some surveillance systems cover high-risk or specific population groups, requiring special reporting methods. Examples are military populations, hospitals, day-care centers, and homes for the elderly. Most surveillance systems incorporate a list of reportable diseases, but the focus of the reporting may be on specific disease entities, such as congenital defects as a reflection of the impact of rubella and cytomegalovirus infections [28].

An example of surveillance in a special population and location is CDC's school-based Youth Risk Behavior Survey (YRBS) [21]. In this survey, questions related to viral diseases, for example, HIV, are self-reported by participating high school students.

2.3 Sources of Surveillance Data

A wide variety of data sources are used for surveillance purposes. Some data sources were designed for the purpose of surveillance and are ipso facto "surveillance systems." Other data sources are used secondarily for surveillance. Sources of surveillance data vary from country to country, state to state, and across local jurisdictions. Availability of surveillance data is dependent on resources available to support the system, such as appropriate laboratory facilities and trained personnel. Table 4.1 lists some data sources that are commonly used for surveillance purposes. These sources are consistent with elements of surveillance summarized by WHO [108].

Table 4.1 Selected sources of data for surveillance

1. Viral statistics
2. Reportable disease systems
3. Surveys
4. Sentinel surveillance
5. Syndromic surveillance
6. Registries
7. Laboratory records
8. Pharmacy records
9. Administrative data

2.3.1 Vital Statistics

The oldest form of surveillance is mortality registration. In most countries, death registration is legally required. As a result, almost all deaths are included in the registries. Causes of death listed on the death certificate is dependent on the presence/absence of a physician or family member who is knowledgeable about the health of the deceased; severity of disease, complexity of the disease, associated illnesses, and whether or not an autopsy or diagnostic laboratory testing was performed. For many viral diseases, such as hantavirus, rotavirus, and influenza, only a small percentage of cases are fatal. However, the case fatality rate is high for other viral diseases, such as AIDS, rabies, Lassa fever, and certain hemorrhagic fevers. Thus, occurrence of viral infections is likely underestimated from the death certificate data. However, vital records are important to document severe complications of viral infections. In addition, surveillance from vital records can be useful for comparing viruses. For example, by 2007 in the United States, the number of deaths associated with HIV was lower than the number associated with hepatitis C [59].

Birth certificates are often used to monitor conditions such as congenital defects (due to rubella and cytomegalovirus infection), diseases transmitted from mother to child (e.g., hepatitis B virus infections), and other conditions of newborns that may impact immediate or long-term health status.

2.3.2 Reportable Disease Systems

The reporting of cases of specified infectious diseases also is legally required in most countries. The US National Notifiable Diseases Surveillance System includes over 70 diseases, of which approximately 30 are viral diseases including 6 arboviruses, 6 hepatitides, and 6 types of hemorrhagic fevers. Reportable disease systems form the backbone of surveillance for most state and local health departments and for many CDC programs. The advantages are that (1) reports are usually made by physicians and/or laboratories, (2) laboratory confirmation is generally available, and (3) there is typically an organized system of regional or national tabulation and reporting. The disadvantages are as follows: (1) the absence of some viral diseases from the required list; (2) the notorious underreporting of diseases despite legal

requirements, primarily because of lack of resources to support both reporting and education of physicians about the need to report; and (3) the variability of reporting efficiency from one jurisdiction to another. Lack of rapid, reliable, inexpensive diagnostic techniques also represents a discouraging obstacle to accurate identification and reporting of many viral diseases [17].

2.3.3 Surveys

Many types of surveys of infectious disease have been used in public health. Formal surveys support the collection of standardized information using standardized methods. Although survey data can be collected quickly over a wide geographic area, the cost of data collection may be prohibitive. The National Health and Nutrition Examination Survey (NHANES), conducted by the National Center for Health Statistics, a component of CDC, uses a complex sampling design to collect nationally representative data on the health and nutritional status of the US noninstitutionalized civilian population [16]. NHANES is a source of data for a number of infectious disease programs, mainly because the laboratory and physical examination components allow both confirmation of case status and collection of health information. For example, the Division of Viral Hepatitis at CDC uses NHANES data to estimate the prevalence of chronic hepatitis B and C for the US noninstitutionalized adult populations (see Sect. 3.3.2).

2.3.4 Sentinel Surveillance

Sentinel surveillance is used as a less costly alternative to population-based surveillance. Sentinel surveillance systems collect data from a sample of reporting sites. Generally a select group of reporting sources—hospitals, healthcare providers, agencies—are recruited to report all cases of one or more notifiable conditions. In the United States, sentinel sites report all cases of influenza-like illness to their state health department on a weekly basis. A network of sentinel providers in British Columbia, Canada, demonstrated the usefulness of sentinel surveillance in documenting the effectiveness of influenza vaccine [49].

2.3.5 Syndromic Surveillance

Syndromic surveillance uses clinical information about signs and symptoms of disease, before a diagnosis is made, as an early warning signal of a potential outbreak. Many syndromic surveillance systems use electronic data from hospital emergency room visits. The value of such systems relies on accurate assessment and coding of symptoms, as well as accurate data entry.

2.3.6 Registries

Registries are often established, usually at the state level, to collect information about persons diagnosed with a disease or condition. For example, cancer registries collect information about type of cancer, anatomic location, stage of disease at diagnosis, treatment, and outcomes. Childhood immunization registries maintain a record of vaccinations received by children within the jurisdiction of the registry [19].

2.3.7 Laboratory Records/Investigations

Laboratory identification of the causative agent of many viral infections has become a routine part of clinical care. Laboratory records are especially useful for public health surveillance. Appropriate laboratory facilities and experienced personnel are needed for the isolation and/or serological identification of the majority of viral infections. These may exist in national or regional public health laboratories, in specialized virus diagnostic institutes, or in university settings.

2.3.8 Pharmacy Records/Investigations

Pharmacy data may be used to identify those who are treated for specific diseases, monitor uptake of new medications, and evaluate effectiveness of specific treatments. For example, when treatment for HIV/AIDS first became available, prescriptions for zidovudine were used to identify potentially unreported cases [54].

2.3.9 Administrative Data

These data consist of electronic records prepared usually for billing or other administrative accounting and are sometimes available in a de-identified format and at no cost for public health use. Data from health plans such as Kaiser Permanente, Medicare, and Medicaid have proven to be useful to supplement routine surveillance data. Hospital discharge data, like insurance/health plan data, provide useful information on diagnosis, surgical procedures, other billed treatments, complications, length of stay, laboratory data, and associated costs. In addition to the wealth of data available in these sources, another attraction is that these data are already collected in electronic form, requiring fewer resources to analyze and summarize.

2.4 Surveillance Networks and Health Information Exchanges

2.4.1 Surveillance Networks

Surveillance networks grew out of the need for a more global approach to surveillance of infectious diseases. Surveillance of infectious diseases was often inadequate in the developing world due to a lack of resources and public health infrastructure. The need for early warning of outbreaks of emerging and reemerging diseases led the Federation of American Scientists to support the establishment of the first infectious disease network, the Program for

Monitoring Emerging Diseases (ProMED-mail) in 1993 [74]. ProMED-mail is an Internet-based system for reporting and disseminating information on infectious diseases outbreaks and acute exposures to toxins that impact human health. This open-source network receives reports from clinicians, public health officials and epidemiologists, laboratory scientists, medical missionaries, journalists, and laypersons. The editors also search the Web and press reports for information. A panel of experts screens, reviews, and investigates reports before they are posted to the website. ProMED-mail allows comparison of reports by geographic location. Thus, users of the system can identify similar outbreaks in both space and time.

Other surveillance networks include Canada's Global Public Health Intelligence Network (GPHIN) [75] and the World Health Organization's Global Outbreak Alert and Response Network (GOARN) [103, 104].

GPHIN, started in 1999, monitors internet websites, news wires, and other internet media to gather and provide information on disease outbreaks and other public health events. This network collects information about infectious diseases, outbreaks, contaminated food and water, natural disasters, bioterrorism events, and safety of products, drugs, and medical devices. GPHIN is part of GOARN [75].

GOARN, started in 2000 by WHO, links existing networks of government and academic centers of excellence, networks of laboratories, medical centers, scientific institutions, and other international organizations. The goal of GOARN is to provide countries with resources and expertise necessary to respond to infectious disease outbreaks. GOARN provides and coordinates technical support, investigates the event, assesses risk, streamlines processes to rapidly deploy field teams, and supports national preparedness [103, 104].

CDC surveillance systems may be viewed as networks connecting the Federal agency with local, state, and territorial health departments and international partners. A number of these surveillance networks focus on viral diseases. An example is the Influenza Surveillance Program [18]. The program which started in 1972 collaborates with local, state, and territorial health departments, clinical laboratories, healthcare providers, and emergency departments to collects and analyzes information on influenza in the United States. Information is collected from five categories of influenza surveillance: viral surveillance, including surveillance for novel influenza A viruses; outpatient illness surveillance; mortality surveillance; hospitalization surveillance; and geographic distribution. Information from these five categories of surveillance is used to track influenza-related illnesses and deaths and to provide a comprehensive overview of activities. CDC also collaborates closely with WHO in global surveillance, including surveillance for novel influenza viruses and in influenza vaccine strain selection.

WHO's Global Influenza Program provides technical support and guidance to Member States and maintains global surveillance for influenza. Virologic and epidemiologic data are collected from countries, areas, and territories through the influenza surveillance and monitoring system. Two platforms are provided for data collection and sharing: FluNet for virologic data and FluID for epidemiologic. These systems allow tracking of global trends, spread, and impact of influenza [106].

2.4.2   Health Information Exchanges

During the late 1900s and early 2000s, there were concerns about the ability of the United States to respond to possible acts of bioterrorism. Beginning with the anthrax attacks shortly after the September 11, 2001 destruction of the World Trade Center, epidemics of such emerging viral infections as West Nile virus, avian influenza, and SARS became a major issue in protecting the health of all Americans [58]. In response, the President of the United States signed Executive Order 12225 on April 27, 2004, which created the Office of the National Coordinator of Health Information Technology (ONCHIT) [58]. The primary objective of this order was to formalize the administration of the office and to advance the development and growth of health information technology as vital to improving the quality of healthcare while reducing its cost. The first step in the process to achieve this critical objective was to use medical records maintained by healthcare providers to build a national network of electronic health records on the majority of Americans, by the year 2014 [13].

Health information exchange (HIE) can be described as the "electronic movement of health-related information among organizations according to nationally recognized standards" developed by the Health Resources and Services Administration (HRSA) [92]. HIE encompasses two major concepts: the electronic sharing of health-related information among organizations and an organization that provides services to enable the electronic sharing of health-related information [15, 46]. The primary goal of HIE is to facilitate access to and retrieval of patient clinical data to provide more efficient, timely, effective, equitable, and safe healthcare. HIE secondary goals are to improve bidirectional communication, to enhance case reporting, and to focus on technology, interoperability, utilization standards, and harmonious collaboration between all patient-centered healthcare providers [13, 97]. The potential of HIEs to integrate the electronic transfer of vital health information among providers and public health agencies is critical in the effort to improve healthcare quality and increase safety for patients [46].

In 2007, CDC funded Health Information Exchanges to support situational awareness project [12]. The objectives of this project were to connect public health providers and organizations

with HIEs in order to improve public health with real-time awareness of the health and status of healthcare facilities within communities, bidirectional communication between healthcare entities, and enhanced case reporting [93]. An example of a successful merge of a HIE with a state partner is the Indiana Health Information Exchange (IHIE) [40, 48]. The IHIE displayed the interoperability of health information exchange by incorporating clinical messaging service (DOCS₄DOCS®) to improve communication between healthcare providers and public health agencies. With this system, clinical result messages can be forwarded to all physicians or targeted to clinical practices or specific geographical areas [90]. In 2009 and 2010, the DOCS₄DOCS® public health messaging system was utilized to alert nearly all physician practices and public health agencies about H1N1 influenza, a syphilis outbreak, an update on rabies treatment, and new vaccination requirements for school children [48].

Another example of a successful HIE is the Northwest Public Health Information Exchange (NW-PHIE) in Washington and Idaho states [90]. This HIE evaluated new influenza surveillance efforts and compared these with existing influenza surveillance data feeds through the Influenza-Like-Illness Network (ILINET). Results indicated that the NW-PHIE data were timelier, more stable, more extensive, and more broadly representative of the community. The NW-PHIE data accurately reflected trends in ILINET activity at the state and community levels [13].

HIEs benefit public health by improving the safety of patients and ensuring quality of healthcare. HIEs augment patient safety by serving as the connecting point for a standardized, organized process of data exchange across regional, state, and local jurisdictions; reducing duplication of services which may result in lower healthcare costs; reducing operating costs by automating many day-to-day organizational tasks; providing management of the data exchange process; and, most importantly, improving communication between providers and patients [46, 93].

3 Seroepidemiology

3.1 Introduction

Seroepidemiology is the systematic collection and testing of blood samples from a target population, or a sample of a population, to identify current and past experiences with infectious diseases by means of biological markers (i.e., antibody, antigen, or other tests). Findings from the tests are the outcomes that, when analyzed, are used to describe patterns and potentially identify factors associated with the outcomes. Seroepidemiologic studies are used worldwide to measure and characterize infectious diseases in the population. Sources of seroepidemiologic data are widely available and

may be collected for other purposes (e.g., blood donor screening), but can be useful for public health purposes. In the context of viral infections, seroepidemiology serves at least three objectives:

1. To supplement surveillance data and inform immunization and public health planning programs
2. To generate hypotheses about the potential association between risk and occurrence of viral infectious diseases
3. To assess old and newly recognized viruses in different population groups

Just as epidemiology is concerned with the occurrence and distribution of clinical cases in different populations, serological epidemiology is concerned with the occurrence and distribution of various components of the blood that indicate past or current infection, that are biochemical markers for certain chronic infections, or that reveal the genetic attributes of strains in various population groups. The epidemiologic characteristics are detected in the laboratory rather than at the bedside; thus, laboratory support is fundamentally necessary to conduct seroepidemiologic surveys. Fortunately, laboratory testing is a part of routine clinical care and is readily available in most countries.

Largely based on the availability of resources to monitor any given viral infection, we might consider that seroepidemiologic data can be classified as:

1. The primary objective of the survey (i.e., a planned and designed survey or study)
2. A secondary use of specimens or data collected for other purposes (i.e., screening programs including blood donors, clinics for high-risk individuals, and other remnant sera)

As a primary objective, serological surveys are frequently integrated with other public health efforts. This section considers the history, methods, and uses of seroepidemiology as either a primary or secondary objective of data collection. As in the surveillance section, we draw heavily on the experience in the United States, but recognize excellent seroepidemiologic studies conducted in other countries.

3.2 Historical Background

The introduction of serological tests for the diagnosis of disease provided the basis for later serological surveys. As early as 1916, the Wassermann test was applied routinely to patients attending a prenatal clinic at Johns Hopkins Hospital by Williams [102] but this was more of a case-finding procedure than an attempt to delineate disease patterns. In 1930, the development of a neutralization test for poliomyelitis led Aycock and Kramer [4] to use the procedure to define the immunity pattern of a given population; this is a landmark in the history of serum surveys. In 1932, Soper et al. [85] mapped out the occurrence of yellow fever in Brazil by

antibody surveys under the auspices of the Rockefeller Foundation, and this technique has been widely used subsequently in studying arbovirus infections. Antibody surveys for influenza also date back to the mid-1930s. The discovery of swine influenza virus by Shope [83] in 1931 and of human influenza virus by Smith et al. [84] in 1933 was rapidly followed by population studies to measure antibody to these viruses among persons of different age groups [2, 9, 37].

The Yale Poliomyelitis Study Unit under Dr. John R. Paul employed serological survey techniques as early as 1935, and his analysis with Riordan of the poliomyelitis pattern in Alaskan Eskimos is a classic study [71]. He became one of the foremost users and promoters of the concept of serological epidemiology, and through his work and writing [69, 72], the utilization of this technique in public health practice and research studies has become a reality. The World Health Organization also took note of this development in 1960 and established three WHO Serum Reference Banks to practice and promote seroepidemiology in New Haven, Connecticut; Prague, Czechoslovakia; and Johannesburg, South Africa. An additional bank was established in 1971 in Tokyo, Japan. The activities and principles of these banks have been reviewed in two *WHO Technical Reports* [105, 107], in a book [72], and in several other publications [70, 73, 81]. Although WHO no longer formally supports these banks, the rationale for proper collection, cataloging, and storage of specimens for use by both primary and collaborating investigators has gained wide application in public health and academic research institutions. For example, WHO collected sera from household surveys in rural areas for the evaluation of the effectiveness of penicillin in mass eradication programs for yaws [42].

Seroepidemiologic techniques were critical to the discovery by Blumberg et al. [7] in 1965 of a particular antigen in the serum of an Australian aborigine; it was uncovered in the course of genetic studies of β-lipoprotein. Since the agent from which the antigen was derived could not be isolated or cultivated in the laboratory, serological surveys using immunodiffusion tests were carried out to detect its presence in the sera of different population groups and different disease entities. The results provided the sole initial evidence that this "Australia antigen" was associated causally with hepatitis B or "long-incubation hepatitis" [8]. Herpes viruses, HHV-6 and HHV-7, were not immediately recognized in association with previously defined disease entities, although the former has been unequivocally shown to be the major, if not the only, causal agent of exanthema subitum.

Many countries recognize the value of such biological resources and have created sizable repositories of serum and, increasingly, tissue or other cellular material containing nucleic acid suitable for molecular and genetic analysis. Seroprevalence studies of many different infections and from many countries have been published.

3.3 Methodology

3.3.1 Ethical Issues

Seroepidemiologic studies were used early in the HIV epidemic because there was a need to determine the unbiased frequency of infection in different populations. A series of serosurveys were conducted to cover different populations including persons attending STD clinics [100], childbearing women [43], and youth training programs [23]. To protect the identity of infected persons, these surveys were conducted anonymously and data were unlinked, such that notifying the person whose blood was tested was not feasible. The ethical issues discussed over time are described by Fairchild and Bayer [36]. The issues included participant consent, the participant's right to know and to control their information, and the responsibility of the health officials to inform the individuals of their test results. When treatment became available, serosurveys continued as long as voluntary counseling and testing was available to survey participants. As clinical data became a more complete source of similar surveillance information, the use of serosurveys became ethically indefensible [36].

Currently, in the United States, Federal Regulations (45 CFR 46.111) require that studies involving human research subjects satisfy the following rules: (a) risks to participants are minimized; (b) risks to participants are reasonable relative to anticipated benefits, if any, to participants, and the importance of the knowledge that may reasonably be expected to result; (c) selection of participants is equitable (i.e., could any special problems arise when research involves vulnerable populations, such as children, pregnant women, fetuses, prisoners, mentally disabled persons, economically or educationally disadvantaged persons); (d) informed consent will be sought from each prospective participant or the participant's legally authorized representative; (e) informed consent will be appropriately documented; (f) the research plan makes adequate provisions for ensuring the safety of participants; and (g) there are adequate provisions to protect the privacy of participants and to maintain the confidentiality of data. Institutions conducting epidemiologic studies maintain "Institutional Review Boards" to ensure that investigators address the above ethical requirements.

3.3.2 Statistical Considerations

When serosurveys are designed as primary data collection, representativeness of the population is usually desirable. In the United States, NHANES combines interviews, physical examinations, and laboratory specimens from a nationally representative sample of about 5,000 persons each year. These persons are located in different geographic areas called primary sampling units, of which 15 are visited each year. Health interviews are conducted in respondents' homes, whereas health measurements are collected in specially designed and equipped mobile centers.

NHANES uses a complex sample survey design [16]. Primary sampling units are generally single counties, where the sampling frame is all counties in the United States. The additional stages of selection in the probability design consist of clusters of households, where each person in a selected household is screened for demographic characteristics, and one or more persons per household are selected for the sample. As with any complex probability sample, the sample design information must be used when undertaking statistical analysis of the NHANES data. In particular, sample weights and the first stage of the cluster design need to be considered. Participants are compensated for participation and receive a report with their health results.

For rapid surveys or for surveys in developing countries, WHO has developed methods for cluster sampling that are more easily implemented and analyzed than multistage probability sample surveys [5]. Using this method, and assuming the survey is conducted to meet several health information needs, the first step is to plan carefully to ensure best use of resources. Sampling is conducted in several stages, starting with regions of a country, then districts within regions, then communities (e.g., villages, blocks, etc.) within the districts and households within the communities. Ideally, the community sampling framework should be a list of all the communities in the region, and there should be a measure of the population size of the community in order to sample with probability proportionate to size. This assessment is helpful because weighting at the time of analysis then becomes unnecessary. The total population divided by the number of communities to be selected determines the sampling interval, which will be used to select the communities after a random start. Also ideally, there is enumeration of the households within the selected communities such that a simple random sample can be selected. If that framework is not available, methods from the 30×7 Expanded Program on Immunization can be used since the selection of households is conducted in the field using a central start; interviews are conducted until information on seven children aged 12–23 months are completed [22, 45]. A slight modification to the above rapid method is "compact segment sampling," proposed by Milligan et al. [62]. In this method, the communities to be sampled are divided into segments of equal population size; then, one segment is randomly selected and all households in the segment are included in the sample.

An important analysis issue for sample surveys of any methodology is whether data have been collected consistently over time. When the same items have been collected using consistent methods, comparisons can be made over time, adjusting for the distribution of the age of the population.

3.3.3 Sources of Biological Material

When serostudies are designed for primary data collection, the collection of blood specimens can be targeted to a carefully and statistically selected sample of the population of

Table 4.2 Sources of human biological materials for surveillance where planned serum surveys from targeted populations are the primary objective

Objective	Sources of biologic materials
Primary	Planned serum surveys from target populations
Secondary	Entrance and periodic examinations of different groups (military, industry, health clinics)
	Blood donors in Red Cross and similar programs (e.g., transplantation donors)
	Public health laboratories:
	Serological tests for HIV (e.g., premarital)
	Other immunologic and diagnostic tests
	Healthcare facilities:
	Entry tests for blood chemistries or syphilis
	Diagnostic tests for infectious diseases
	Blood banks and transplantation programs
	Prenatal; clinics (e.g., hemodialysis)
	Employee health services
	Counseling and testing sites, clinics for sexually transmitted diseases
	Drug treatment clinics

interest. To achieve efficiencies from this type of study, serological surveys should be multipurpose in nature and can include measurement of antibodies, genetic material, and other clinical laboratory markers of health or illness. In the United States, the NHANES has produced a nationwide population-based health profile for more than two decades. As one of its many components, it has provided valuable seroprevalence data on a variety of viral infections, for example, measles, poliomyelitis, herpes simplex virus (HSV), hepatitis A virus (HAV) [53], and HBV [98].

A list of several sources of material for survey analysis is shown in Table 4.2. Examples of sources of specimens for secondary use include blood collected for routine tests during physical examinations for the armed forces or industry or during an outpatient visit or admission to a hospital and from neonates screened for specific heritable disorders. Sera sent to a public health laboratory for serological tests for syphilis, viral diagnosis, or other diagnostic tests have also been employed. These collections of sera may not be representative of the age, sex, and geographic distribution of the entire population; the nature of the biases introduced must be recognized and evaluated. However, they are economical to obtain and sometimes may reveal important information about the presence or absence of a certain virus in the community or about the occurrence of a recent outbreak. An example of this type of serostudy was the description of the frequency of HIV and hepatitis B and C infection among injection drug users in several US cities [63].

Specimen Management. The collection and management of specimens depends on the type of specimen (e.g., viruses might be identified in stool samples, oral swabs). For blood, the specimen must be collected and separated under sterile

conditions. Aliquots of 0.5 ml each have been used by the WHO and CDC and are very useful for microtiter tests; several replicates of the entire collection may be prepared at the time of aliquoting so they can be shipped to other laboratories for testing. Sera are usually stored at −20 °C, often in a commercial warehouse. Temperatures of −70 °C are best but are more expensive to maintain. Lymphocytes can also be separated from anticoagulated blood, frozen at low temperatures in fetal calf serum and dimethyl sulfoxide (DMSO), and later thawed for examination of stable cell surface markers and other cell-associated products. Cellular material, even in extremely low concentration and a nonviable state, may be quite suitable for amplification and identification of fragments of nucleic acid. These techniques offer powerful tools for detecting genes characteristic of specific infectious agents and other biological material of interest.

3.3.4   Laboratory Tests

The general principles and techniques of laboratory testing for viral infections are presented comprehensively in Chaps. 2 and 3 of this text. The antibody tests most suitable to serological surveys of specific viruses are detailed in each corresponding chapter of this book. The criteria for a satisfactory test include simplicity, sensitivity, specificity, reliability, ability to detect long-lasting antibody, minimal interference from nonspecific inhibitors, the availability of satisfactory reagents, and the safety of the test for the laboratory technician [29, 107]. The microtiter procedure developed by Takatsy in 1950 in Hungary and popularized in this country by Sever [82] in 1962 has become the standard method in serological survey laboratories. It is adaptable to a wide variety of antibody determinations, it requires a minimal amount of serum (usually 0.1 ml) and other ingredients, and large numbers of sera can be efficiently tested. Several automated methods of dilution and of adding various reagents have been introduced to speed the testing even more [107].

The development of simple tests such as the enzyme-linked immunosorbent assays (ELISA) for antibody measurement in microtiter plates has provided a sensitive method for identification of antibody in serum samples from survey populations and can indicate both past and current infections [109]. The use of monoclonal antibodies in this and other antibody tests permits highly specific identification of individual strains of the virus, a special advantage in determining whether a new strain has been introduced in a community or if reinfection or reactivation has occurred in the individual. Commercial kits for many antibodies are now available, and new formulations are continually being devised for a variety of clinical, public health, and research applications. Detection of virus and genetic characterization of viruses can be accomplished using polymerase chain reaction (PCR) methods. Handling of specimens for PCR depends on two components: the source and virus, for example, varicella zoster

virus can be identified in dried blood specimens, which can be stored at ambient temperature indefinitely. In general, PCR requires specialized kits that differ for qualitative or quantitative detection. Sequencing of select regions of amplified genetic material can be used to describe strains of virus circulating in a region or country; however, because of cost, these methods are frequently restricted to determine transmission during investigations of acute clusters of disease [1].

A full list of laboratory tests conducted using specimens collected as part of the NHANES 2009–2010 can be found here: http://www.cdc.gov/nchs/nhanes/nhanes2009-2010/lab_methods_09_10.htm.

3.4   Advantages and Limitations

The use of serological surveys is an important means of supplementing morbidity information, such as that obtained from routine case surveillance. Advantages are listed in Table 4.3. Because many viral infections may be clinically mild or inapparent, laboratory confirmation is necessary for accurate diagnosis of even overt cases. Data from serological surveys can reveal *total* burden of infection (apparent and inapparent), both currently and in the past. Selection of tests that reflect antibody of long duration permits measurement of the cumulative experience of the population tested with the disease in question; selection of a test based on short-lived antibody such as immunoglobulin M (IgM) allows identification of a recent infection or epidemic. Testing of two sera spaced in time permits measurement of the incidence of infection during the interval period.

An important advantage of carefully planned prospective serosurveys is that participants can become a cohort for other studies. For example, to determine the frequency with which hepatitis C-infected persons in the United States were aware of their infection, the National Center for Health Statistics conducted a follow-up survey of positive cases. A full interview with these participants yielded not only awareness, but also whether they sought medical care for their infection and their knowledge, attitudes, and practices related to hepatitis C [25].

Table 4.3 Advantages and limitations of seroepidemiologic studies by data collection objective

	Primary	Secondary
Advantages	Sample is representative of the target population	Less expensive
	Many possibilities of lab markers and behaviors	Saves time
		No participation bias from volunteers
Limitations	Expensive and labor-intensive	Convenience sample might not be representative of the population of interest
	Time consuming to design and implement	

An advantage of serostudies in providing information to guide vaccination programs is that serostudies measure immunity and are likely more reliable than self-reported vaccination coverage [26]. Another advantage is that aliquots of sera from a collection can be shipped, frozen, over long distances to a number of specialized reference laboratories for testing; therefore, the work can be divided among participating laboratories.

The disadvantages of seroepidemiology are the cost, time, and effort involved in the selection of the target population, the collection and analysis of data and blood, and the need for and cost of laboratory facilities equipped to carry out the tests. There must also be a satisfactory means of measuring antibody for the particular virus to be studied, and the method of carrying it out must be simple enough to allow performance on a large-scale basis. Finally, because serostudies designed for primary data collection are labor-intensive and prospective, there are significant delays in the availability of data. For example, the NHANES data require about 2 years between the end of data collection and the availability of datasets for public use.

3.5 Uses of Serological and Molecular Techniques

3.5.1 Prevalence

Prevalence from serosurveys, or seroprevalence, is defined as the number of persons whose sera contain a particular biomarker among the total number of persons examined at that point in time (frequently, 1 year). Unlike "case prevalence," which indicates the existence of disease at the time of the survey, the presence of antibody reflects the cumulative experience, past and present, with an infectious agent. The prevalence is a function both of prior and current infection and of the duration of the antibody tested. In contrast, antigen indicates presence of the virus at that time; in cases of latent or asymptomatic infection, it indicates prevalence of chronic infection.

Many antibodies such as the neutralization antibody for poliomyelitis or yellow fever virus; antibodies to the HIV core, polymerase, and envelope; and the hemagglutination-inhibition antibody for influenza, parainfluenza, rubella, measles, or arboviruses last for years, perhaps a lifetime. Thus, the cumulative experience of a population can be measured and infection acquired in childhood can be detected in persons of middle or perhaps even old age. Some waning of antibody titers (sometimes below the lowest detectable levels) may occur in older age groups after a childhood infection or vaccination. Similarly, the viral capsid antigen (VCA)-IgG antibody to Epstein–Barr virus measured by the indirect immunofluorescence test has been found to be of long duration; even

complement-fixing antibodies to cytomegalovirus, herpes viruses, or dengue virus have been found to persist for years following infection.

Measurement of IgG and IgM antibody by tests such as the ELISA or immunofluorescent antibody tests provides a simple way in a single serum sample of reflecting current and past infection, respectively. Although IgM antibody usually denotes a primary infection, certain viruses such as herpes viruses may induce IgM on reactivation. It should also be reemphasized that unlike prevalence data for clinical infectious disease, serological prevalence data reflect total infection rates, representing both clinical and subclinical (or asymptomatic) infections.

Multipurpose antibody surveys have been carried out in a number of countries. In the United States, the successive NHANES surveys have provided large numbers of serum specimens for estimating cumulative exposure to various infections in representative samples of the population. For example, NHANES was critical in an understanding of hepatitis A immunity in the United States because a vaccination program was initiated in 1996 targeting select higher incidence areas. Stratifying seroprevalence by country of birth and race/ethnicity (Fig. 4.1) showed the higher levels of immunity among foreign-born and US-born Mexican Americans of any age. The impact of the initial vaccination strategy was evident in an analysis of seroprevalence stratified by geographic region and age group (Fig. 4.2) [53].

In a Barbados seroprevalence study [32], a 10 % household sample was randomly selected from a middle- and lower-socioeconomic-level community of 10,000 persons in Bridgetown. The results illustrate the type of information that can be derived from this type of study. Of 100 sera from children under age 10 tested, 30 % lacked protective levels of antitoxin against both diphtheria and tetanus, indicating the need for intensifying the immunization program against these diseases. The prevalence of protective levels against tetanus is a good indicator of the level of public health practice, since this antitoxin is acquired almost exclusively by immunization procedures and not through natural infection. The age distribution of antibodies to various viruses may provide useful information on the behavior of these infections in the community and of the need for immunization programs. On this basis, an active rubella immunization program was initiated in girls aged 12 years or younger. In subsequent years through 1978, a few sporadic cases were reported yearly, but no epidemic occurred [34]. Even sporadic serosurveys have demonstrated utility, for example, the researchers from the Barbados effort conducted a similar survey in St. Lucia [31]. They found important and unexpected differences compared to Barbados, including a higher prevalence of antibodies to dengue and rubella among young persons.

Fig. 4.1 Age-specific seroprevalence of antibodies to hepatitis A virus by country of birth and race/ethnicity, NHANES, 1999–2006
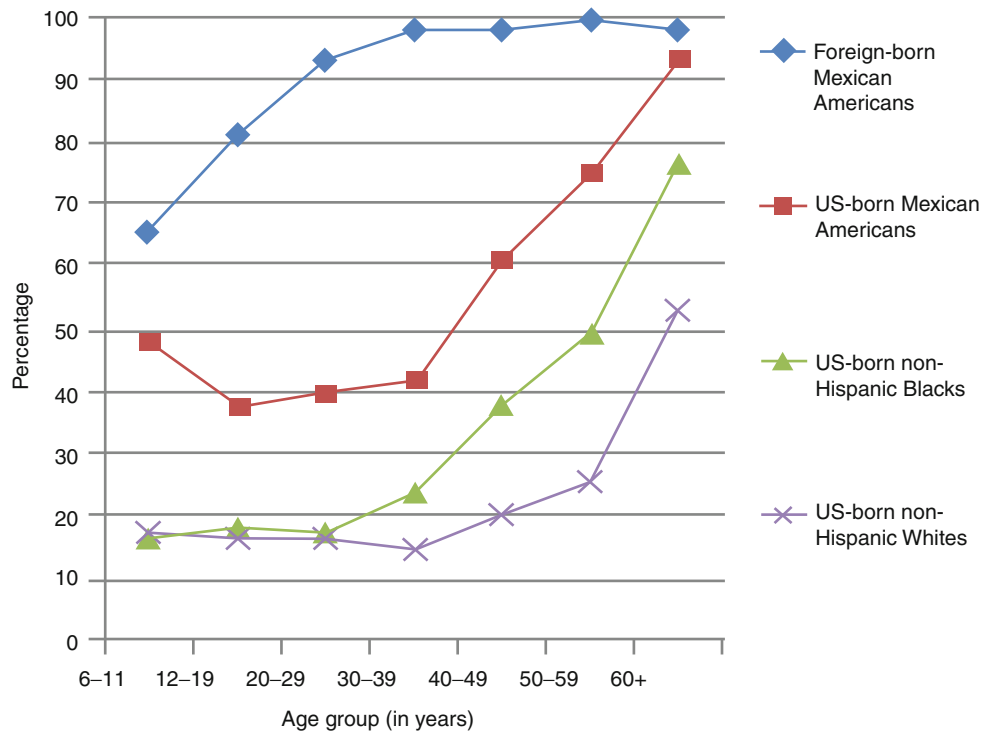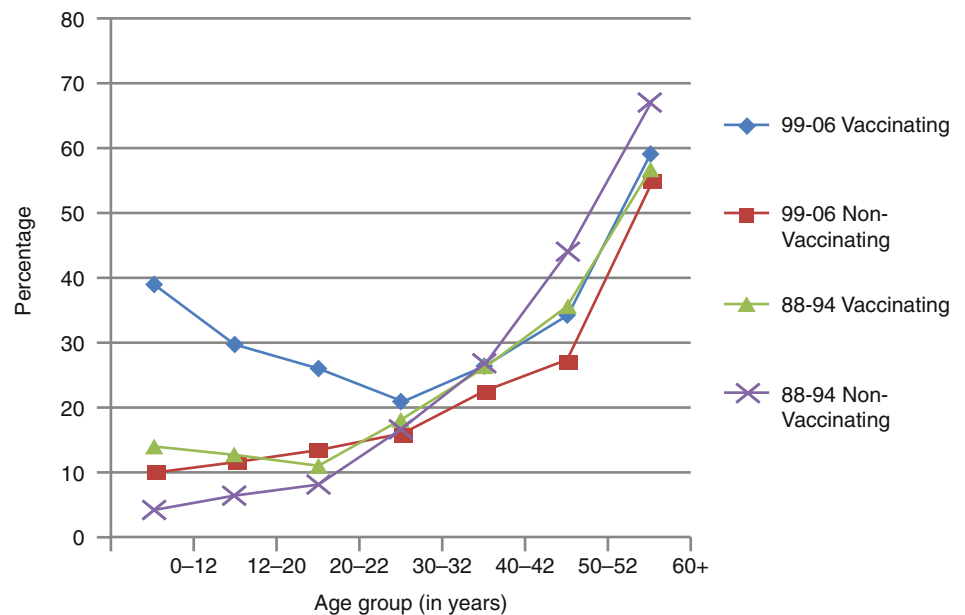

Fig. 4.2 Age-specific seroprevalence of antibodies to hepatitis A virus among US-born people by residence in vaccinating or non-vaccinating states based on 1999 recommendations, NHANES, 1988–1994 and 1999–2006

Initial tests for poliomyelitis antibody employing conventional microtiter neutralization procedures indicated that 27, 42, and 54 % of those tested at 1:5 or 1:8 serum dilution lacked antibody to poliomyelitis types 1, 2, and 3, respectively [32]. Subsequent tests on 304 sera using a 1:2 serum dilution and longer serum–virus incubation periods indicated that only 13.1 % lacked type 1 antibody, 6.5 % type 2 antibody, and 14.3 % type 3 antibody [34]. This emphasizes the need for sensitive methods for detecting low levels of antibody. Two mass poliomyelitis programs were carried out

after the 1972 survey, one in 1974–1975 and another in 1977–1978. There have been no reported cases of poliomyelitis since 1972.

The 1972 Barbados serum collection was tested for human retroviruses after the agents were discovered. The HTLV-1 antibody was found in 4.25 % overall, rising in age from a 2.7 % prevalence for persons aged ≤10 years to 9.0 % among those aged 61–70 years [78]. Females had a higher prevalence rate (5.8 %) than males (2.3 %). The adult pattern raised the possibility of sexual transmission, and this was

strengthened by the finding of a prevalence rate of 14.1 % among persons with a positive VDRL test for syphilis as compared with 3.5 % of those who were VDRL negative. There was evidence of household clustering and of vertical transmission.

Advances in laboratory detection of viruses in oral fluids allow surveillance in high-risk groups with less-invasive techniques. For example, unlinked anonymous surveillance among injection drug users seeking services in England and Wales has been ongoing since 1990 [88]. The authors found that the prevalence of hepatitis C infection decreased from 70 % in 1992 to 47 % in 1998 before rising again to 53 % in 2006. Prevalence among women injecting drug users was higher than among men, and that prevalence was highest in certain geographic areas that could be targeted for prevention.

3.5.2 Incidence

Incidence is best calculated from cohort studies such that the appearance of the viral infection can be captured with a known denominator of a well-defined population of persons at risk. However, cohort studies are costly and subject to attrition over time.

Many prospective serological and clinical studies were used to investigate HIV infections and the development of AIDS and related clinical syndromes among high-risk populations such as gay men, injection drug users, persons with hemophilia, and their contacts. Some of the earliest studies were based on cohort methods using sera originally collected for evaluation of HBV vaccine, and others started afresh with a new cohort [50]. The findings in the New York [86] and San Francisco cohorts [10] were as follows: (1) the prevalence level of HIV antibody was 6.6 % in New York at entry into the study in 1978, and rose to 10.6 % by 1984; (2) in San Francisco the entering prevalence was 4.5 % in 1978, but rose dramatically to 73.1 % by 1985; and (3) the rate of viral infection (seroconversion) among those lacking antibody on entry was 5.5–10.6 % per year in New York and 11.2 % in San Francisco. Among gay and bisexual men entering the Multicenter AIDS Cohort Study (MACS) in Baltimore, Chicago, Los Angeles, and Pittsburgh in late 1984 and early 1985 [50], seroprevalence ranged from 23 to 49 %. In a pattern similar to those in other cohorts, the incidence rate of new infection in the MACS, documented at 3–5 % per year in early 1985, declined rapidly during the next 3 years to about 1 % [52]. In Africa and Thailand, measurements of seroprevalence and incidence among prostitutes and other high-risk groups have repeatedly demonstrated the alarming increases that have taken place over a very few years. Transfusion-associated HIV infection systematically documented through serosurveillance of hemophiliacs and other recipients [3, 54, 55], soon after known parenteral exposure, provided an important resource for comparative research on the natural history of HIV infections and the development of AIDS. Further details of serological studies of HIV infection can be found in Chap. 43.

The calculation of incidence is possible from such cohort studies because clinical, laboratory, and self-reported data are collected on participants at regular intervals. Therefore, negative results are available, such that a time period can be calculated between the first positive and the most recent previous negative result. Taken together, these and other cohort studies have yielded critical data for the empirically based projections about burden of infection and disease in select populations.

3.5.3 Outbreak Detection

The advances in genetic characterization and communication online have combined to expand the scope and breadth of serosurveillance into early detection of clusters of infectious diseases. In the United States, norovirus is the most common cause of foodborne disease outbreaks. Surveillance to detect early clusters of disease is conducted through routine notifiable diseases methods and by a laboratory network called CaliciNet [96]. It is a national surveillance network that includes a database for public health laboratories to submit gene sequences from human caliciviruses (noroviruses and sapoviruses) identified from outbreaks. The information is used to link norovirus outbreaks that may be caused by common sources (such as food), monitor trends, and identify emerging norovirus strains.

Measles in the United States provides an excellent example of the use of technology in outbreak detection. In 2000, the United States achieved measles elimination (defined as interruption of year-round endemic measles transmission) (http://www.cdc.gov/measles/global-elimination.html). However, importations of measles into the United States continue to occur, posing risks for measles outbreaks and sustained measles transmission. During 2011, a total of 222 measles cases (incidence rate: 0.7 per one million population) and 17 measles outbreaks (defined as three or more cases linked in time or place) were reported to CDC, compared with a median of 60 (range: 37–140) cases and four (range: 2–10) outbreaks reported annually during 2001–2010.

Measles has also reappeared in other developed countries, and a web-based, quality-controlled database with epidemiologic and nucleotide data for measles infection in the WHO/Europe region was developed: the Measles Nucleotide Surveillance (MeaNS) [60, 79]. The major objectives of the MeaNS initiative are to function as an epidemiologic surveillance tool and to monitor progress in measles control. Dynamic reports and graphical charts can be created on any user-selected fields in the MeaNS database (e.g., genotype or sequence variation in a geographical location or time period). Information about MeaNS is available at http://www.hpa-bioinformatics.org.uk/Measles/Public/Web_Front/main.php.

3.5.4 Diagnostic Serology

Sera sent to large hospitals or public health laboratories for various tests can be frozen and stored for later antibody testing against other antigens. The specimens must be adequate in amount and free of bacterial contamination. Specimens sent for viral antibody tests usually fulfill these criteria and are accompanied by minimal demographic and clinical data concerning the patient. There are many uses for this type of collection. All sera or exanthems coming from patients with central nervous system, gastrointestinal, or respiratory infections can be tested at the time of receipt or, later, against a battery of viral antigens in order to reveal the profile of agents likely to have caused the syndromes. An example of this was the evaluation of the importance of a new virus, called "the California encephalitis virus" in the causation of infections of the central nervous system by testing of all sera received in a state public health laboratory for this syndrome [44]. In Wisconsin, 5.7 % of 351 sera received in the state laboratory over the period 1961–1964 revealed evidence of the new California viral infection [91]; in Minnesota, 4.1 % of 1,617 retrospectively tested sera contained this antibody. A second and related application is the determination of the clinical spectrum associated with a newly discovered virus; this is accomplished by testing stored sera from patients with a variety of clinical syndromes and looking for evidence of infection with the new agent.

A third application for sera stored over time is the measurement of *secular trends* or antigenic shifts in viruses over time. This is especially useful in relation to influenza viruses. A fourth use, employing freshly received sera from high-risk populations, is the search for influenza antibody patterns that may reveal the beginning of an outbreak or a change in the antigen composition of currently circulating strains; this was used by Widelock et al. [101] at New York City public health laboratories. Comparison of the geometric mean antibody titer to influenza sera from persons in the acute phase of an unidentified respiratory illness with the titer in others convalescing from a similar illness may permit early identification of an outbreak without waiting for serial samples from the same persons.

Finally, investigators in South Australia made efficient use of samples taken in conjunction with blood donation. They searched for evidence of Ross River virus activity in different locations during the arbovirus season by measuring IgA-, IgG-, and IgM-specific antibody in samples from Red Cross blood donors. Differences in antibody prevalence by region indicated prior activity and helped identify endemic areas but revealed that acute infection had not occurred in that year at frequencies high enough to be detected [99].

3.5.5 Evaluation of Immunization Programs

The effectiveness of an immunization program is traditionally judged on the basis of clinical cases or epidemic behavior. A program is regarded as effective when cases decrease or epidemics do not occur. This information may be biased by the possibility that the decrease in clinical cases is related to poor reporting or that insufficient time has elapsed for another epidemic to have occurred. Currently, our knowledge of the utilization of vaccines depends on such sources as sales records of manufactures, public clinic and physicians' data, direct interviews, and school entry surveys [20]. Because of the inadequacy of these traditional surveillance techniques in determining the need for and the effectiveness of a given vaccine, serological surveys could play an even larger role in evaluation of immunization programs. Although the necessity for a venipuncture reduces the ease and acceptability of this method, public health professionals and physicians can help surmount such barriers by conveying the importance of seroepidemiology for such purposes. Newer techniques that obviate the requirement for blood sampling may further encourage the application of biological tools to the evaluation of vaccination effectiveness.

The uses of serological epidemiology in immunization programs are summarized in Table 4.4. Much of this information could be obtained in no other way. Serological surveillance has been of particular importance for the new epidemiologic settings created by substituting vaccine immunity for natural immunity as for poliomyelitis, measles, rubella, and to a lesser extent mumps and influenza [30]. With vaccines against HBV universally recommended for infants in the United States and a vaccine against varicella zoster virus, the patterns of susceptibility to and the distributions of these infections have changed substantially.

Table 4.4 Uses of seroepidemiology in immunization programs

1. Cross-sectional surveys to determine the need for immunization programs in:
(a) Different age groups
6–20 months—measure duration of maternal antibody
School/college entry—identify omissions, failures, loss of protective antibody
(b) Different geographic areas
(c) Different socioeconomic groups
(d) High-risk occupational groups
2. Follow-up measurements in immunized persons to determine:
(a) Proportion developing local, humoral, cell-mediated immune responses
(b) Quality and extent of response
(c) Nature and degree of interaction between vaccine components
(d) Duration of response
(e) Level of protection against disease and asymptomatic infection
(f) Degree of spread of live vaccine strains to exposed and susceptible contacts
3. Periodic serological surveillance to identify groups who are not receiving vaccines or who have inadequate responses

Patterns of susceptibility and immunity to all of these viruses may now vary from place to place, from age group to age group, and in various socioeconomic settings, depending on the immunization program instituted by health departments and the activities of physicians and clinics rather than on the inherent epidemiologic characteristics of the natural infection and disease. The methods of immunization practice, the frequency of repeated immunization programs, and the quality and duration of vaccine immunity will increasingly constitute the major determinants of the patterns of these diseases.

Over the years, serological surveys in American cities, such as Syracuse [56], Cleveland [38], and Houston [61], have uncovered serious deficiencies in the antibody patterns for viral diseases for which vaccines are available. The US military has used this approach to similar advantage. A national serosurvey of 1,547 Army recruits entering in 1989 at ages 15–24 years documented 15–21 % seronegativity for measles, mumps, and rubella; 7 % for varicella zoster virus; and 2.3, 0.6, and 14.6 % for poliovirus types 1, 2, and 3, respectively [51]. Likewise, a pre-vaccination survey of 1,568 US Navy and Marine entrants identified important differences in susceptibility to measles; susceptibility was greatest among males, younger recruits and whites [87]. Serosurveillance has also been used effectively in the developing world for such purposes as a general assessment of success in the WHO Expanded Program on Immunization [35] and a specific comparison of HIV-infected and uninfected Zairian infants for responses to polio vaccine [80]. The importance of surveillance programs and serological surveys to evaluate immunization programs has long been recognized [30, 47]. Thanks to testing of antibodies to hepatitis B that allow distinguishing immunization (where antibodies to hepatitis B surface antigen are positive and antibodies to hepatitis B core are negative), from past or from chronic infection, seroprevalence in NHANES has guided the US vaccination program for hepatitis B. Wasley et al. compared findings from the 1999–2006 NHANES with previous surveys and found that a history of infection with HBV had decreased from 1.9 to 0.6 % among children. Prevalence of antibodies consistent with immunization increased from 20.5 % in 1999–2002 to 25.2 % in 2003–2006 [98].

Hepatitis B also was examined in a study of data from 10 European countries. Residual sera were combined with sera from samples available at national serum banks [65]. Testing assays and algorithms were standardized to allow cross-country comparisons. The authors also collected information on country-specific vaccination policies. Six of the ten countries reported low levels (<3 %) of antibodies to hepatitis B core antigen. Of the eight countries testing for HBV surface antigen (HBsAg), Romania had the highest prevalence (5.6 %); the remaining seven countries had prevalence <1 %. Countries can apply findings from such comparisons to modify and adjust their own vaccination policies.

3.5.6   Biomarkers

Revolutionary advances in immunology and molecular biology have opened the possibilities for intensive analysis of humoral and cellular material—what some are calling broadly "molecular epidemiology"—analysis that will clarify the role of viral infection in the pathogenesis of autoimmune, degenerative, neoplastic, and even "genetic" diseases and will facilitate targeted drug and vaccine development. An example of one such possibility for molecular study is a European network for hepatitis B virus. The HepSEQ (http://www.hepseqresearch.org) is a pioneering online resource for the management, characterization, and tracking of hepatitis B infection in the area. An important use will be to detect mutations of the hepatitis B virus such as those consistent with antiviral resistance [64]. This information will be helpful in identifying transmission patterns that will guide prevention efforts.

4   Summary

Systematic collection of cases of infection or disease and of biomarkers of infection or immunity is an essential tool in the prevention and control of viral diseases. Surveillance and seroepidemiology have provided critical epidemiologic information to support public health policy at the local, national, and international levels. Continued advances in laboratory methods and communication systems will expand the applications of surveillance and refine their precision and efficiency.

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