Original Contribution

Epidemic Assistance by the Centers for Disease Control and Prevention: Role of the Epidemic Intelligence Service, 1946–2005

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Since 1946, the Centers for Disease Control and Prevention has responded to urgent requests from US states, federal agencies, and international organizations through epidemic-assistance investigations (Epi-Aids). The authors describe the first 60 years of Epi-Aids, breadth of problems addressed, evolution of methodologies, scope of activities, and impact of investigations on population health. They reviewed Epi-Aid reports and *EIS Bulletins*, contacted current and former Epidemic Intelligence Service staff, and systematically searched the PubMed and Web of Science databases. They abstracted information on dates, location, staff involved, health problems, methods, and impacts of investigations according to a preplanned protocol. They assessed the methods presented as well as the quality of reports. During 1946–2005, a total of 4,484 investigations of health events were initiated by 2,815 Epidemic Intelligence Service officers. In the early years, the majority were in response to infectious agents, although environmental problems emerged. Investigations in subsequent years focused on occupational conditions, birth defects, reproductive health, tobacco use, cancer, violence, legal debate, and terrorism. These Epi-Aids heralded expansion of the agency's mission and presented new methods in statistics and epidemiology. Recommendations from Epi-Aids led to policy implementation, evaluation, or modification. Epi-Aids provide the Centers for Disease Control and Prevention with the agility to respond rapidly to public health crises.

Centers for Disease Control and Prevention (U.S.); population surveillance; preventive medicine; sentinel surveillance

Abbreviations: CDC, Communicable Disease Center (now the Centers for Disease Control and Prevention); EIS, Epidemic Intelligence Service; EISOs, Epidemic Intelligence Service officers; Epi-Aid, epidemic-assistance investigation.

In 1946, the US Congress established the Communicable Disease Center (CDC) to support state health departments in controlling communicable diseases (1). A critical part of this support was technical assistance, initially in the form of laboratory expertise and vector control necessary to support the agency's initial mission to combat malaria in the southeastern United States. By 1949, under the guidance of Alexander D. Langmuir, MD, epidemiologic support became the critical consultative tool, and epidemic-assistance investigations (Epi-Aids) became the most visible program of the new agency. The system of epidemiologic support was formalized by Langmuir in 1951 with establishment of the Epidemic Intelligence Service (EIS) Program (2).

Although the CDC (now the Centers for Disease Control and Prevention) works with health agencies throughout the world in multiple ways, the term *Epi-Aid* refers to investigations of serious and urgent public health problems in response to formal requests for rapid assistance from states, federal agencies (e.g., the Indian Health Service, the National Institutes of Health, the Food and Drug Administration, and the US Department of Defense), international organizations (e.g., the World Health Organization), and ministries of health from other countries. Certainly, extensive service is provided by EIS officers (EISOs) and other CDC staff outside the formal Epi-Aid mechanism, including the majority of the work performed by officers and staff assigned to states and international settings.

For example, the 1955 investigation of polio vaccine contaminated with live virus involved essentially all EISOs and was conducted both in the field and at CDC headquarters,

yet it was never classified as an official Epi-Aid (3). Two other studies illustrate such service in later years. A 1983 study led by an EISO using data from a multicenter case-control study documented the high risk of pelvic inflammatory disease for women using the Dalkon Shield intrauterine device and recommended that all women using the device have it removed (4). An investigation led by an EISO assigned to the state health department documented the transmission of cryptosporidium infection through the public water supply in Milwaukee, Wisconsin, that led to an outbreak of disease affecting more than 400,000 residents and subsequent modifications of water quality standards (5). Nevertheless, this critical mechanism of response remains a symbol of the CDC and EIS: rapid response to a public health need whenever and wherever it is detected.

As inaugurated in 1946, Epi-Aid responses still are documented by an initial announcement, the Epi-1, followed by a report of the investigation, the Epi-2 (now called the Epi Aid Trip Report), and sometimes later reports (Epi-3s and Epi-4s), all of which are addressed to the CDC Director and relevant staff at the requesting agency and at the site of the investigation (6). These documents are labeled *for administrative use*, *limited distribution* and *not for publication* because results are preliminary and might contain identifying information about patients, providers, and institutions. Meanwhile, Epi-Aids provide a rich chronicle of the practice of field epidemiology at the CDC since 1946 and often are key events that marked the evolution of the agency and public health practice (refer to Appendix Table 1).

Use of the Epi-Aid mechanism expanded dramatically after establishment of the EIS Program, which provided a pool of field epidemiologists in training who were available to depart immediately for an investigation anywhere in the world. The success of the EIS Program, in part enriched by the availability of the Epi-Aid mechanism, plus the expansion of the CDC mission over time has resulted in more than 3,000 epidemiologists being trained (7). The initial class of 23 men included 22 physicians and a sanitary engineer. In contrast, the majority of the 2009 and 2010 EIS classes of 75–80 members are women and include at least 10 foreign citizens. Approximately 30% of the US citizens are members of racial/ethnic minorities, and 50% are physicians. The majority hold a master's or doctorate degree, and the others hold a mixture of doctorates in multiple disciplines or are veterinarians, dentists, and nurses.

In this report, we describe the first 60 years of Epi-Aids. We highlight the breadth of health problems as the CDC's mission expanded; the evolution of the epidemiologic, statistical, and information display tools; the national and global scope of activity; and the impact of these investigations on the health of communities.

MATERIALS AND METHODS

We reviewed bound copies of all Epi-Aid reports maintained by the CDC's Public Health Library. In addition, we reviewed available copies of *EIS Bulletins* and contacted current and former EIS supervisors and officers in an attempt to locate published reports based on the epidemiologic investigations. We also identified related publications through online searches

of the PubMed and Web of Science databases (updated January 22, 2009). We abstracted information according to a preplanned protocol and included relevant dates, location, staff involved, and suspected or confirmed health problems (Table 1). In addition, we reviewed laboratory, statistical, and data presentation methods as well as recommendations and impacts on health resulting from the investigations.

To assess the statistical and other methodological characteristics of EIS investigations, we adapted a rubric for assessing published statistical practice (8). We used this rubric to code all reports on Epi-Aids according to statistical and other methods presented. Types and frequencies of applied methods were classified systematically into 17 categories (Table 2). Reports containing analyses beyond descriptive ones were classified as basic, intermediate, or advanced according to the sophistication of applied statistical techniques. Reports using stratification, nonparametric methods, one-way analysis of variance, simple correlation, and regression were counted as intermediate analyses. Reports containing any method of multivariate analysis, statistical modeling, advanced contingency table analysis, or survival analysis were categorized as advanced analysis. For this report, we did not implement a rigorous assessment of quality of statistical methods applied; however, we do comment on different aspects of methodological quality.

RESULTS

During the 60 years from 1946 through 2005, EISOs and their colleagues initiated investigations of 4,484 health problems in every state and globally (Figures 1–3).

Geographic patterns

During the early years, the geographic distribution of Epi-Aids was a function of location of the CDC facilities as well as population. Since 1946, the CDC facilities outside Atlanta, Georgia, have been located in Alaska (current), Arizona, California, Colorado (current), Kansas, Maryland (current), Montana, New Mexico, North Carolina (current), Ohio (current), Pennsylvania (current), Puerto Rico (current), Texas, Washington (current), West Virginia (current), and Washington, DC. The District of Columbia and 6 states did not invite the CDC for Epi-Aids during the first decade, including New York (the most populous state at the time), Massachusetts, Connecticut, Rhode Island, Wisconsin, and South Dakota, but all states and the District of Columbia had one or more requests during each of the 5 subsequent decades. The first response to a health concern outside the United States was after a flood in Canada in 1950. As the CDC's international presence became known, 493 international requests for assistance followed from 13 world regions (Figure 3).

Types of problems investigated

First decade. During the initial decade, 1946–1955, a total of 110 of 136 (81%) epidemic assistance requests were conducted after the EIS Program was established in July 1951, and all but 3 were conducted in response to infectious agents. Interestingly, a 1946 investigation of dysentery in

Table 1. Classification and Number of Health Problems Addressed in Epi-Aids, 1946–2005

|	1946–1955	1956–1965	1966–1975	1976–1985	1986–1995	1996–2005	Total
Infectious disease							
Bacterial	31	171	362	309	312	284	1,469
Mycobacteria	1			7	57	57	122
Mycoplasma			5	2	2	3	12
Chlamydia				1	3	1	5
Spirochete					4	14	18
Virus (HIV)[a]	74	231	313	246 (1)	202 (3)	170 (13)	1,236 (17)
Parasite	8	10	92	50	42	41	243
Fungus	2	5	10	14	19	24	74
Multiple pathogens	8	4	4	1	3	6	26
Pseudoepidemic			14	7	10	1	32
Other		1	2	1	3	8	15
Program evaluation					8	21	29
Surveillance						7	7
Chronic disease							
Cancer		7	78	27	5	2	119
Diabetes			1		5		6
Cardiovascular				2		2	4
Neurologic			4	1			5
Nutrition					4	9	13
Tobacco				5		1	6
Program evaluation					9	2	11
Law evaluation					6		6
Maternal and child health			19	22	10	14	65
Genetic			1	2			3
Birth defect		2	5	11	14	8	40
Other			3	6	6	4	19
Environmental/injury							
Environmental	3	11	18	107	70	66	275
Refugee health assessment				2	1	4	7
Famine				1			1
Drug/vaccine reaction		4	17	12	9	10	52
Contaminated drug/complication of treatment				1	1	2	4
Error in commercial product preparation			1			1	2
Poisoning/toxin			16	10	1		27
Illicit drug use			1	4	5	2	12
Unintentional injury				3	13	11	27
Intentional injury/terrorism			1	5	13	14	33
Insect bite							
Other							
Hysteria			4	2	1	2	9
Syndrome	8	35	76	101	69	32	321
Unknown			3	10	3		16
No. of Epi-Aids[b]	136	500	1,077	1,018	907	846	4,484

Abbreviations: Epi-Aids, epidemic-assistance investigations; HIV, human immunodeficiency virus.

[a] The numbers in parentheses are not included in the virus total.

[b] These numbers also include Epi-Aids that were discontinued or consolidated into one investigation.

Table 2. Classification and Number of Methods Used in Epi-Aids, 1946–2005

Year	1946–1955	1956–1965	1966–1975	1976–1985	1986–1995	1996–2005
Total no. of Epi-Aids	136	500	1,077	1,018	907	846
No statistical methods	88	325	506	229	11	29
Data collection						
Surveillance		19	11	70	128	435
Case series	5	3	50	11	24	26
Survey	12	38	103	257	67	232
Randomization		2	3	22	4	7
Complex sample		1	6	7	5	15
Power calculation				5	3	24
Descriptive statistic, estimate						
Mean, median, mode, percentage	18	27	324	584	181	554
Measure of variability (variance or confidence interval)		7	70	357	112	432
Risk						
Attack rate	26	90	203	239	73	210
Odds ratio		1		41	56	238
Risk ratio				60	39	141
Case-fatality rate	1	5	3	18	8	20
Mortality rate	1		3	13	1	13
Birth rate	1		1			1
Fetal death rate			1	2		1
Etiologic fraction/attack risk			2		3	6
Inferential methods						
t test/z test		1	15	91	13	15
Basic (chi-square, Fisher's exact)	8	18	132	382	59	141
Advanced (Mantel-Haenszel and other)	1	1	1	44	10	60
P value, method unknown		12	81	66	60	328
Poisson			17	31	5	6
Binomial				30	2	4
Observed/expected	2		29	19	4	5
Regression			2	41	3	7
Logistic regression				24	14	104
Survival analysis			1	6		2
ANOVA/ANOCOVA						6
Time series					1	
Nonparametric						
Mann-Whitney				53	1	3
Kruskal-Wallis				6	6	36
McNemar			1	26	1	5
Wilcoxon				30	16	54
Other						
Natural experiment			1			
Vaccine efficacy			6	12	1	17
Focus group			2	2	1	5
Economic analysis				9	7	17
Environmental analysis					56	246

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; Epi-Aids, epidemic-assistance investigations.
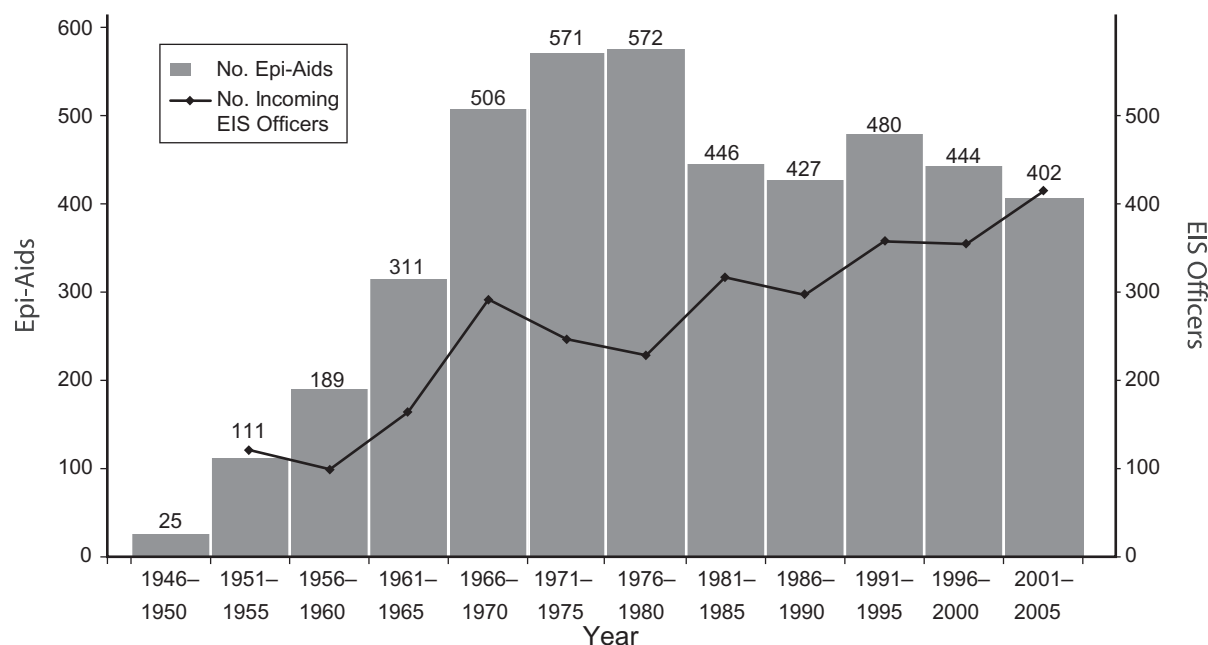
Figure 1. Number of epidemiologic-assistance investigations (Epi-Aids; *N* = 4,484) and incoming Epidemic Intelligence Service (EIS) officers (*N* = 2,815), by year, 1946–2005.

Texas was conducted jointly by the CDC (then the Malaria Control in War Areas Program) and the National Institute of Health (established in 1930; became the National Institutes of Health in 1968). The first Epi-Aid to include an EISO was a 1951 response to equine encephalitis in Virginia. A chief EISO was appointed in 1952, and, by August of 1953, an EIS unit had been established at the CDC. The term *germ detective* was used first in a 1954 Epi-Aid concerning an undiagnosed rash in Kentucky.

Early Epi-Aids provided the foundation for later methodological developments to address emerging health problems and organizational decisions. In 1947, a response to hepatitis in Georgia included an innovative analysis of racial disparities. A 1948 investigation of diphtheria in Montana resulted in a recommendation that a full-time health department be established in that state. We identified the first peer-reviewed publication that resulted from a 1949 investigation of western equine encephalitis in Colorado (9). Recommendations from an Epi-Aid to investigate impetigo in a laundry associated with a neonatal ward in 1949 provided the foundations for the CDC's hospital infection prevention activities.

The first example of a health communication professional participating in an investigation occurred during a 1950 Epi-Aid addressing polio in Ohio; this investigation subsequently was covered in *Life Magazine* (10). During that period, more diseases were identified as the CDC added programmatic responsibilities and increased laboratory capacity, and environmental problems began to be reported. For example, a 1953 Epi-Aid documents the death of a child at the Mayo Clinic in Rochester, Minnesota. The cause was initially thought to be trichloroethylene exposure but later was determined to be caused by agranulocytosis from an unknown contaminant in raw milk.

Second decade. The number of Epi-Aids increased to 500 during 1956–1965. Occupational conditions appeared in Epi-Aid files in 1957, when workers in a garment factory suffered from heat exhaustion and anxiety. In 1964, we have the first Epi-Aid concerning birth defects; in that same year, an outbreak initially reported as fatty degeneration syndrome was probably among the first reported cases of Reye syndrome.

Forty-three outbreaks of suspected polio were confirmed in 21 investigations during the decade after vaccine availability, often among vaccinated populations. The CDC responded with stockpiled oral polio vaccine. Indeed, a 1961 Epi-Aid documented the highest recorded incidence of polio in West Germany, probably attributable to live vaccine. In 1964, the EIS investigation of the first adverse reaction to live virus polio vaccine was reviewed by a blue-ribbon panel that included Albert Sabin.

In 1956, Epi-Aids involved EISOs in the first isolation of the virus causing St. Louis encephalitis from a bird in nature, the first outbreak of turkey ornithosis in which human cases occurred among persons not involved in processing work, and the first outbreak of hepatitis in the United States attributable to a municipal water supply. In 1957, an Epi-Aid resulted in the first report of inhalation anthrax in modern world literature. The first identification of type E botulinum toxin came from an Epi-Aid in Michigan in 1963, and, in that same year, an Epi-Aid investigation of the first reported localized outbreak of *Neisseria meningitidis* group B at a
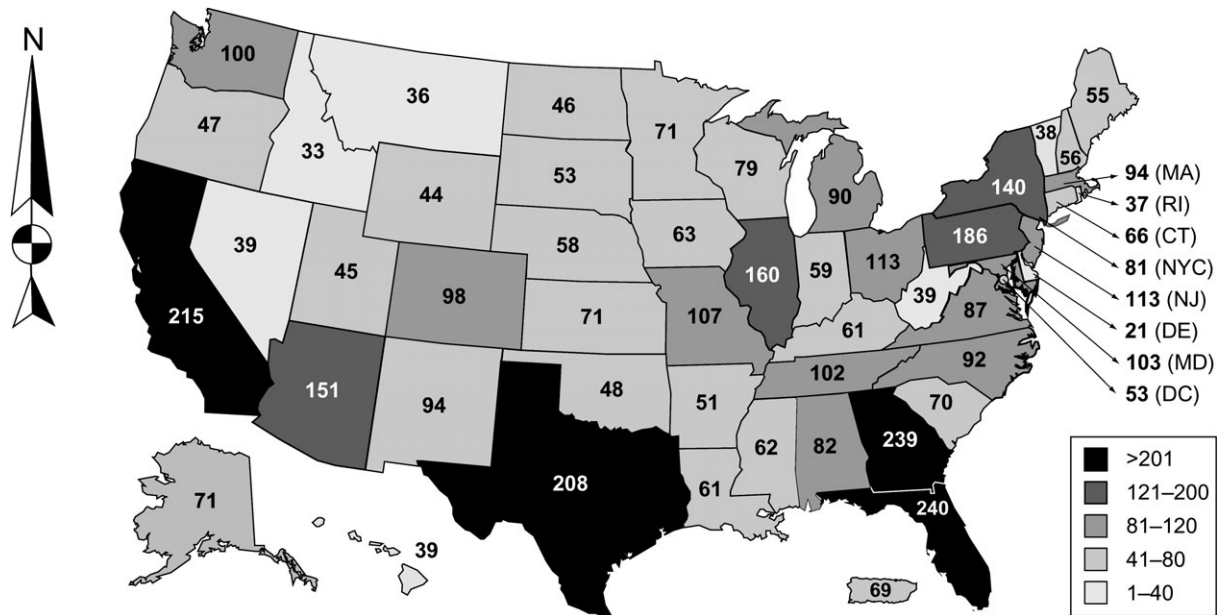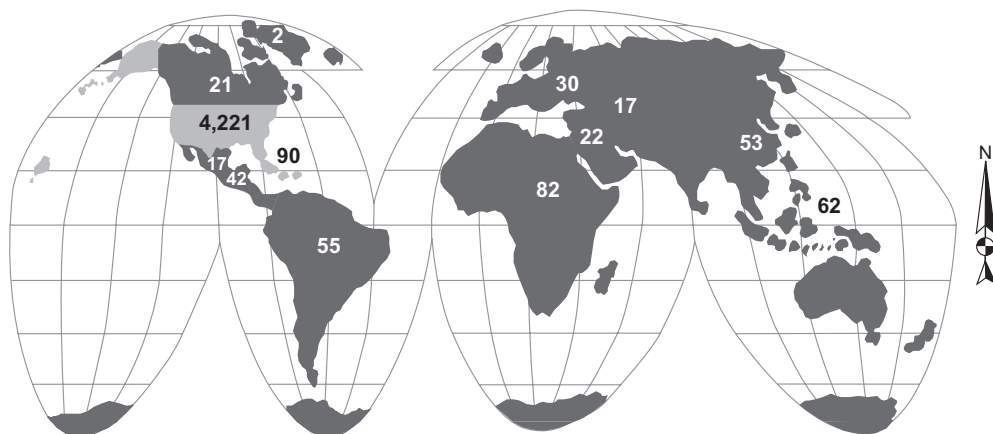
Figure 2. Number of epidemic-assistance investigations by US state, the District of Columbia (DC), and Puerto Rico, 1946–2005. The numbers exclude 25 epidemic-assistance investigations whose scope was national. Many investigations were multisite. CT, Connecticut; DE, Delaware; MA, Massachusetts; MD, Maryland; NJ, New Jersey; NYC, New York City; RI, Rhode Island.

California naval base demonstrated failure of antimicrobial prophylaxis.

Throughout the second decade, Epi-Aids thrust EISOs into the midst of legal debate. For example, a 1960 investigation of hepatitis caused by drug toxicity was postponed because of legal concerns. In 1963, an investigation of illness associated with an industrial cafeteria resulted in litigation brought by the employees against management, and an outbreak of food-borne illness resulted in a lawsuit against the grocery chain distributing the product. Of note is that, as commissioned officers of the US Public Health Service, EISOs need permission from the US Surgeon General to testify in a court of law, which limits their availability for testimony.

Third decade. During 1966–1975, EISOs and their colleagues investigated 1,077 reported health problems (Figure 1), an increase of more than 100% over the previous 10-year period. Botulism was suspected in 55 Epi-Aids; of these, 26 were confirmed food botulism, 2 were wound botulism, 1 was a laboratory incident, and the other suspect cases were found to have multiple etiologies (e.g., Guillain-Barré syndrome). In 1 of the botulism investigations, the father and mother of a family of 4 moving from Oklahoma to Colorado were found dead in their car, and their 19-year-old daughter was comatose for 14 days before recovery. Apparently, the family had eaten contaminated meatloaf brought on the journey. Other investigations of suspected botulism among people

Figure 3. Number of epidemic-assistance investigations worldwide, 1946–2005. Many investigations involved more than one country. Puerto Rico is included in the US total of 4,221, and the number 90 includes countries and other territories in the Caribbean.

in a car in 1967 and 1970 ultimately were determined to have been caused by carbon monoxide poisoning; the investigations documented increased susceptibility to carbon monoxide among smokers.

In a 1965 investigation, an outbreak of pneumonia at a Washington, DC, hospital seemed to be caused by exposure to the hospital grounds, but no etiologic agent was identified. A 1967 investigation of an outbreak of febrile myalgia was determined to be related to the air-conditioning in the Pontiac, Michigan, health department, which also led to illness among the EISOs; again, however, the etiologic agent was undetermined. (In 1976, an Epi-Aid in Pennsylvania led to identification of *Legionella pneumophila* by the CDC laboratorians as the causal agent in all 3 outbreaks, as well as a 1957 Epi-Aid in a Minnesota meat-packing plant.)

The CDC's role in the Global Smallpox Eradication Program had a profound and lasting effect on the agency. During 1966–1972, 11 domestic and 6 international Epi-Aids were initiated for smallpox or cowpox; however, only in the 6 international Epi-Aids was smallpox confirmed or surveillance activities initiated where disease was known to be prevalent. Typically, the cause of the other cases was chickenpox or insect bites. Smallpox eradication campaigns involved EISOs in Ghana, India, and Yugoslavia. Other international Epi-Aids required EISOs to investigate emerging hemorrhagic fevers in Germany (Marburg virus, 1968) and Sierra Leone (Lassa fever, 1972).

Development of the CDC's Chronic Disease Program evolved from a 1961 investigation of acute lymphocytic leukemia in Illinois. Interest in chronic disease persisted throughout the decade—77 cancer clusters were investigated (the vast majority were leukemia), as well as cardiomyopathy and diabetes. Attention was directed toward broader aspects of reproductive health and family planning beginning in 1966. Investigations related to maternal death from abortion and increased incidence of abortion led to an evaluation of family planning services in New York in 1971. During this decade, 19 investigations involved aspects of reproductive health; 19 others involved birth defects.

Also during the third decade, EISOs moved into other fields of public health (e.g., the epidemiology of illicit drug use and violence, infectious complications of needle sharing by intravenous drug users (1970 and 1971), and heroin-related overdose deaths in Georgia (1972)). In 1973, an EISO investigated homicides in Atlanta.

Fourth decade. During 1976–1985, EISOs and their colleagues investigated a total of 1,018 reported health problems, a number comparable to that in the previous 10-year period, but with the size and complexity of the investigations reaching new levels. New infectious problems initially investigated as Epi-Aids included Legionnaires disease in 1976 and Ebola hemorrhagic fever in Zaire and Sudan in 1976. In 1981, an investigation of Kaposi's sarcoma and *Pneumocystis carinii* pneumonia represented the initial investigation of what would become known as acquired immunodeficiency syndrome, and, in 1985, an Epi-Aid was conducted to study a cluster of deaths related to conjunctivitis among children, later termed Brazilian purpuric fever.

Attention to social and behavioral aspects of health also evolved during this decade. For example, in 1976, the asso-ciation of binge drinking with bacterial infections was noted among American Indians. A 1977 analysis of health effects of drought in Haiti included income as well as more innovative measures of socioeconomic status, and the investigator recommended that a refugee unit be established at the CDC. In the first Epi-Aid regarding unintentional injuries caused by motor vehicles in 1983, increased mortality was related to 3-wheeled all-terrain vehicles in Alaska. Testimony before the Consumer Product Safety Commission led to a nationwide ban on these vehicles. EISOs were dispatched to solve problems involving mysterious circumstances, including a 1977 investigation of cardiac deaths associated with a popular liquid protein diet, unexplained sudden deaths among Hmong refugees in 1981, and infant deaths from digoxin overdose associated with a hospital nurse in 1982.

Fifth decade. The 907 Epi-Aids conducted during 1986–1995 involved substantial and increasingly complex health problems. For example, a 1991 Epi-Aid involved more than 100,000 reported cholera cases in Peru, the first time the disease had been discovered in that country during the 20th century and an event marking the beginning of a new cholera pandemic. Also in 1991, an Epi-Aid documented the first cholera outbreak in the United States associated with a commercial product, a coconut milk topping.

During a decade highlighted by emerging infectious diseases, Epi-Aid investigations uncovered the first human case of *Salmonella enterica* serotype Newport associated with antibiotic use in animals (1986); the first occurrence of meat as a vehicle for *Listeria monocytogenes* (1989); the first confirmed case of human ehrlichiosis (1986); and the first outbreak caused by *Escherichia coli* O104:H21, a non-O157, Shiga-like toxin-producing *E. coli* (1994). Investigation of a 1987 epidemic of cholera in Guinea Bissau confirmed that those who had eaten rice and fishmeal prepared by the same persons who had prepared an epidemic victim for burial were at increased risk. In 1990, EISOs discovered that apple cider can carry *E. coli* O157:H7, and, 3 years later, an Epi-Aid identified hundreds of confirmed cases of bloody diarrhea and dozens of cases of hemolytic uremic syndrome caused by *E. coli* O157:H7 associated with consumption of undercooked hamburgers sold at the Jack-in-the-Box (San Diego, California) fast-food chain.

In addition to these advances in infectious conditions, the percentage of Epi-Aids related to disabilities, injuries, environmental exposures, cardiovascular disease, and other chronic diseases increased. The first physical-activity-related Epi-Aid in 1986 assessed the impact of a community-based exercise program; a 1993 survey of tobacco outlets revealed that the majority of them sold to minors despite laws forbidding such sales. Hurricane Andrew stimulated an acute response in 1992, with long-term follow-up the next year. An Epi-Aid in Philadelphia, Pennsylvania, confirmed more than 600 deaths resulting from heat exposure in Philadelphia in 1994; a year later, an investigation of heat-related deaths in 4 states uncovered 465 deaths in Chicago, Illinois, and 85 in Milwaukee during 3 days. In 1988, an Epi-Aid in Georgia noted that 1.3% of children aged 17 years or younger were confirmed victims of child abuse or neglect, and, during an investigation of school violence in 1995, approximately

60% of students reported having access to handguns and 67% of students favored using metal detectors in schools.

Increasingly, recommendations from Epi-Aids led to federal policy implementation, evaluation, or modification. A 1986 investigation of an epidemic of diarrhea linked to *S. enterica* serotype Enteritidis contamination of commercial pasta led to a labeling change. The Food and Drug Administration recalled L-tryptophan when a series of investigations in 1988–1989 linked it to eosinophilia-myalgia syndrome. A 1990 Epi-Aid evaluated a policy prohibiting tobacco sales to minors; in 1991, another evaluated the effectiveness of anonymous human immunodeficiency virus testing and counseling.

Sixth decade. During 1996–2005, fewer Epi-Aids ($n = 846$) were requested, probably reflecting increased state and local health department capacity as well as more field-based EISOs, but an increase in multistate and nationwide investigations was also evident. Several events led to the largest deployments in the history of the program—the attack on the World Trade Center in New York City and anthrax-tainted letters in 2001, and the devastation of Hurricanes Katrina and Rita in 2005. During 2001, a total of 126 EISOs were deployed one or more times in multiple Epi-Aids to New York City; Florida; North Carolina; Washington, DC; and Connecticut. In 2005, a total of 28 officers participated in 115 individual deployments to Louisiana, Mississippi, Alabama, and Texas, focusing on rapid needs assessment, public health surveillance, infection control in evacuee shelters, health needs of displaced persons, and environmental effects. These 2 events were dramatic examples of the evolving role of EISOs in major health threats facing the nation.

Two infectious disease events might have highlighted any other decade had they not been overshadowed by terrorism and disasters. The first was the introduction of West Nile virus in New York City in 1999 and its subsequent systematic march across the country in ensuing years. The threat posed by this virus was anticipated in a 1996 Epi-Aid that identified more than 500 suspect West Nile virus cases in Romania. During 1999–2002, a total of 19 West Nile virus–related Epi-Aids were conducted in New York, Louisiana, Mississippi, and Arkansas. The second event, the devastation wrought by the newly identified coronavirus that causes severe acute respiratory syndrome led to 2 Epi-Aids in the United States and 3 in Asia—Vietnam, Taiwan, and Thailand. Three multistate investigations confirmed the strong association (odds ratio = 36) between rotavirus vaccine and intussusception (1999), discovered the association between development of meningitis infection and cochlear implants (2002), and documented transmission of monkeypox from exotic animals sold as pets by a single distributor (2003).

The events of September 11, 2001, were not the only criminal activities that involved EISO investigations. A 1996 Epi-Aid documented acute renal failure attributable to contaminated glycerin being added to acetaminophen syrup in Haiti, resulting in 75 deaths. That same year, epidemiologic data from an Epi-Aid supported a criminal investigation of abscesses in 47 of 69 patients treated with intramuscular adrenal cortex injections by a single physician. A 1997 investigation exposed intentional poisoning of Texas hospital employees who had consumed tainted pastries in a break room, leading to shigellosis among 7 persons. In 1999, Epi-Aids were conducted in response to anthrax threats directed at California clinics performing abortions and in Pennsylvania in response to a cluster of *Serratia marcescens* cases associated with a respiratory technician tampering with equipment.

Food and waterborne disease investigations were more frequently national and international in scope, no doubt reflecting broader societal changes in both the sources of food and dietary preferences. A 1996 Epi-Aid linked 900 cases of gastroenteritis to raspberries from Guatemala contaminated with *Cyclospora* and traced it to birds in the berry fields. A 1998 multistate outbreak investigation for the first time associated *Salmonella* with cold cereal, and the largest outbreak of *E. coli* ever documented in the United States was investigated among an estimated 56,000 persons who became ill after eating at catered events. An investigation in 2000 of a multistate outbreak of 841 cases of *S. enterica* serotype Bareilly from contaminated bottled water convinced the Food and Drug Administration to recall the product. In 2005, EISOs documented the first norovirus outbreak attributed to commercially prepared food (delicatessen-type meat).

By this time in public health, diet, fitness, and recreation were well documented as being necessary for a healthy lifestyle, but EISOs demonstrated that these efforts are not without risk. Health consequences included herpes infection among wrestlers, methicillin-resistant *Staphylococcus aureus* among football players, and cryptosporidiosis among swimmers. Persons from 29 countries and 20 US states who participated in ecoChallenge 2000 contracted leptospirosis, and *Campylobacter jejuni* was identified among bike tour participants from 44 states and Canada in 2003. In addition, military trainees suffered from muscular overuse injuries, and hockey players experienced carbon monoxide and nitrogen dioxide poisoning from incorrect use of an ice resurfacing machine. Efforts to maintain a healthy diet were complicated by widespread *Salmonella* epidemics associated with presliced tomatoes in 2003 and 2004 and with unpasteurized orange juice in 2005, and by the largest hepatitis A foodborne outbreak in US history in 2004, which was associated with green onions. An Internet hoax claiming that necrotizing fasciitis was associated with bananas was disproven by a 2000 Epi-Aid.

The first transmission of Nipah virus from pigs to humans was reported in Malaysia in 1999, recurring in Bangladesh in 2004. In 2001, the Ebola hemorrhagic fever investigation team diagnosed 425 cases and 224 deaths in Sudan and Uganda, the largest documented outbreak of this disease and the first with an onsite laboratory. In 2004, investigations of 317 cases and 125 deaths in Kenya showed that they were related to hepatotoxicity caused by aflatoxin-contaminated maize.

Environmental hazards continued to challenge EISOs as they evaluated allergic reactions to tattoo products in multiple states and assessed access to sidewalks, safety, and ease of walking in West Virginia as part of their obesity prevention activities. Epi-Aids evaluated the effect of President Clinton's welfare reform on access to prenatal care in New York City (1997) and the impact of legislation granting Oregon adoptees aged 21 years or older access to their birth records (2000). The 2004 investigation of 709 migrant deaths (most commonly from heat stroke) within 2 years at the US–Mexico

border documented a serious consequence of illegal immigration. A 2003 Epi-Aid studied the health and behavioral repercussions of the electricity blackout in Ohio, Michigan, and New York.

Methodological concerns

During early Epi-Aids, reported statistical methods were primarily calculations of rates and measures of central tendency (percentages, means, and modes). Data display most often consisted of 1- or 2-way tables. The first use of a frequency distribution occurred in a 1952 Epi-Aid concerning suspected measles. Also in that year, a report on hepatitis in Kentucky contained the first mention of an analysis using punch cards; this report was also the first to use a map. A 1953 Epi-Aid report on encephalitis among Florida horses provided an early cost-benefit analysis, noting in the recommendations that the price of a horse was less than the price of one dose of the recommended vaccine. A social network analysis was used in 1955 to investigate rabies among dogs. By the end of 1955, we began to see sporadic, if not routine, use of epidemic curves.

During 1956–1965, a total of 325 of 500 (65%) reports included no statistical results. Of the remainder, the most frequent statistical methods were summary measures of central tendency (e.g., mean, median, and percentage) or attack rates. Of the 178 Epi-Aids that reported any statistical methods, 85 (48%) collected data through convenience survey methods or used existing surveillance data. Rarely were measures of variability or confidence intervals reported. We located only one analysis that used stratification and no advanced methods.

Still, change was evident during the 1950s. A statistician EISO introduced an innovative measurement of socioeconomic status as a risk factor for illness, and the first anthropologist in the EIS used anthropologic methods in an investigation of polio in Arizona in 1956. Perhaps as a result of increasing diversity of disciplines in EIS, epidemiologic methods advanced as well. The first dose-response analysis occurred during a 1956 investigation of hepatitis in a Texas housing project. A 1957 report of the association of breastfeeding with illness from an investigation of staphylococcus in a newborn nursery was the first to use exclusion criteria, a chi-square statistic, and a P value; the fatality rate was the highest reported to date in the United States. We begin to observe use of odds ratios (1958), stratified analysis (1959), and computers (the IBM (International Business Machines Corporation, Armonk, New York) method, 1959). Randomization methods were reported first in 1961 as the *CDC randomization technique*. Inferential methods appeared as the first use of an epidemic threshold (1962), and the first use of the t test in an Epi-Aid was reported in 1963. In that same year, a pie chart was used for the first time in a report of an outbreak of polio in the Marshall Islands.

Influenced by Langmuir, Epi-Aids often were initiated after review of surveillance data; this was documented in 273 of 1,077 (25%) of all Epi-Aids conducted during 1966–1975. Only 506 (47%) provided no statistical methods compared with 65% during the previous decade. The most frequent statistical methods continued to be summary measures

of central tendency or attack rates. However, during the third decade, data collection methodology in Epi-Aids shifted from convenience survey methods or case-series to case-control or cohort studies. We note the emergence of multivariate methods in regression (1973) and survival (1974) analysis. Nonparametric methods were used first in 1975, and the first use of a focus group in an Epi-Aid investigation was documented during this decade.

During 1976–1985, we observe the increasing sophistication of statistical methods in the first reported use of linear regression (1978), analysis of variance (1976), discriminant analysis (1977), multiple linear regression (1977), a Kolmogorov-Smirnov test (1979), logistic regression (1980), and cluster analysis methods (1980). The first statistical methods section appeared in an Epi-2 in 1977.

In part, the increasing sophistication of statistical methods was a result of the increasing use of computers and software packages, as well as coverage of these topics in the EIS introductory course. Indeed, the first mention of SAS (SAS Institute, Inc., Cary, North Carolina) and SPSS (SPSS, Inc., Chicago, Illinois) software in an Epi-Aid was in 1980 in an investigation of injuries during a prison riot. Quality control for keypunching was reported first in a 1984 suicide study. The first use of a deterministic mathematical disease model in an Epi-Aid, the Reed-Frost model, was reported in a 1985 investigation of a measles outbreak.

Despite this sophistication in methods, we continue to observe reporting of personal identifiers as late as 1985, the lack of statistical methods in 229 (22.5%) of 1,018 investigations during 1976–1985, and a tendency to report P values without accompanying statistical methods in 66 (6%) reports.

New methods continued to be used in Epi-Aids during 1986–1995, including time-series analysis to study food poisoning in Peru (1986), capture-recapture methods to study school-related deaths (1994), record matching to study motor vehicle injuries among older drivers (1995), and generalized estimating equations to study dengue in Palau (1995). Case-control studies became the method of choice during this decade; Epi-Aid reports often used matching techniques. Frequently, both risk ratios and odds ratios were reported. As computer software became more widely used, logistic regression began to replace Mantel-Haenszel adjustment for risk estimates. Unfortunately, power calculations were reported rarely, and still P values often were given without explanation of methods.

During 1996–2005, EISOs increasingly incorporated economic data into their investigations of disasters (1997), coxsackievirus infection (1999), hepatitis A (1999), meningitis (1999), program evaluation (1999), measles (2001), and coccidioidomycosis (2002). Again, during this decade, use of surveillance methods was prevalent; 435 (51%) of 846 Epi-Aids were initiated through review of surveillance data or used surveillance data for analysis. Only 29 (3%) Epi-Aids included no statistical methods in the report.

EISOs continued to explore new methods of analysis: a logic model (1996), Walter's method (11) for cluster analysis (1997) a method for repeated measures (1998) (12), calculations for an overcrowding rate (1999), and a time/space method (2004). As during previous decades, the method for randomization was reported rarely.

DISCUSSION

The data and stories included in the 4,484 Epi-Aids describe a fascinating history, a history elaborated in scientific publications, in multiple books, and frequently in the popular press, the last most notably in the pages of the *New Yorker* magazine by Berton Roueché (13, 14). The importance of this history to the EIS Program and of the 2,815 EISOs to the CDC and to public health is, however, the reason for summarizing the Epi-Aid story in this report.

The reason for absence of Epi-Aids in some US states during certain years was not always clear. Certainly, throughout the years, both state and local health departments developed increased epidemiology and laboratory science capacity. Sometimes the reasons might have been based on local politics or legal considerations. At other times, the absence of Epi-Aids might be attributed to personality clashes or a perception that EISOs or their supervisors did not respect the local needs and constraints. For example, no Epi-Aids occurred in New York State during 1946–1955, and the state health officer, Herman Hilleboe, an assistant surgeon general temporarily assigned to the state, is reported to have said, "I don't want any of Langmuir's storm troopers in New York." More often, the resistance was less explicit and more passive. Nonetheless, the legacy is one primarily of collaboration and mutual respect, and the data support this conclusion.

During the 60 years reported on here, 4,484 Epi-Aids were initiated by 2,815 EISOs (many EISOs participating in multiple investigations). The leveling off in the number of investigations since 1980 paralleled enhanced capacity of public health departments across the United States and increased complexity of investigations conducted by EISOs (Figure 1). During this time, 4,221 Epi-Aids were completed in the United States and Puerto Rico (Figure 2); 493 were conducted in 106 countries and 13 territories (Figure 3).

Naturally, as the Communicable Disease Center until 1970, the CDC focused almost exclusively on infectious disease; only limited numbers of Epi-Aids were not directed to infections (Table 1). Sometimes, outbreaks of unclear cause led to new or unexpected etiologies. The pursuit of an infectious cause of cancers led to more than 100 investigations of clusters during the 1960s and 1970s. No infectious causes were identified, but the effort formed the basis for development of a chronic disease program and, in 1994, formation of the National Center for Chronic Disease Prevention and Health Promotion. Similar efforts to apply epidemiology and surveillance to birth defects and to population concerns were highlighted by Epi-Aids, and programs in women's health and the CDC's National Center for Birth Defects and Developmental Disabilities were established in 2002.

Today, approximately 50% of the CDC's staff and budget remains devoted to combating infectious diseases around the world, but an increased proportion of the work and of the EIS classes is focused on prevention and control of chronic diseases, injuries, environmental health exposures, and noninfectious conditions affecting women and children. The number of Epi-Aids directed to bacterial disease declined from a peak in the decade ending in 1975 but has remained at approximately 300 since then. The number devoted to viral diseases declined at the same time and stabilized at approximately 200 during the past 2 decades, with a similar pattern for parasitic diseases. In contrast, Epi-Aids for mycobacteria, particularly tuberculosis, have increased during the past 2 decades, as have those for chlamydia and fungal infections. The Epi-Aid mechanism has also been increasingly used for urgent program evaluations in those years.

Other than investigations of cancer clusters and problems related to women's and children's health, the Epi-Aid process has had limited application to chronic disease. Similar to investigations of infectious diseases, urgent program evaluation using the tools of an epidemiologist has been adopted some in the past 2 decades, particularly to evaluate laws and policies.

In contrast, Epi-Aids for environmental health and injury events have been used more extensively, starting with the 1950 flood disaster in Winnipeg, Ontario; Langmuir was the consulting epidemiologist. These investigations were often in response to natural and human-made disasters and led to development of standard practices that are now routine in response to floods, heat waves, hurricanes, tornadoes, and other widespread health events. Similar epidemiologic and surveillance methods have been applied to injuries, both intentional and unintentional, with limited but increasing frequency during the past 3 decades.

The evolution of statistical methods in the acute setting of the Epi-Aid reflects a similar pattern in other public health settings (Table 2). Especially notable is the increased use of multivariate modeling beginning in the late 1970s, paralleling advances in computer hardware, especially the laptop, and advances in computer software, most notable CDC-sponsored Epi Info, an open-source software package developed in the 1980s for practicing epidemiologists and now translated into 15 other languages (15).

Epi-Aids provide the CDC with a unique ability to respond immediately to public health crises throughout the United States and internationally. To many people, the CDC's capacity for rapid response symbolizes its, and more particularly the EIS Program's, special role in protecting the public's health. The scope and impact of the EIS Program since its inception in 1951 is reflected dramatically by these investigations. Such investigations are only a part of what the agency and EISOs do; nonetheless, they contribute considerably to the trust in the CDC expressed by the US public and the international community (16). The ability to adapt to new challenges in often uncertain and sometimes hazardous settings is chronicled in these reports. Continuing success of the EIS Program and the CDC depends on the ability to retain that agility and anticipate new challenges. To do so, the CDC must continue to prepare its workforce adequately for future public health needs and to base all its work on the best science available.

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(Appendix follows)

Appendix Table 1. Centers for Disease Control and Prevention Timeline

Year	Key Event
1946	The Communicable Disease Center opens on July 1 in Atlanta, Georgia.
1947	The plague laboratory (California) is transferred to CDC (the first epidemiology unit).
1949	Alexander Langmuir, MD, becomes CDC's chief epidemiologist; CDC is designated the US Public Health Service lead in disaster response as a result of assistance provided to Texas City, Texas, after the explosions there in 1947.
1950	Transfer to CDC of a field station in Kansas City, Kansas (histoplasmosis), with responsibility for Greeley, Colorado (encephalitis), as well as activities in Montana, Puerto Rico (schistosomiasis); field stations in Texas and Arizona are added to study the role of flies in diarrhea and dysentery.
1951	Twenty-two physicians and a sanitary engineer join the first EIS class in July.
1952	The first national conference of state and territorial epidemiologists is held.
1955	The Cutter incident involving contaminated killed polio virus vaccine occurs; the Conference of State and Territorial Epidemiologists is officially organized.
1957	The Asian influenza pandemic influences national guidelines for vaccine use; the Venereal Disease Division is transferred to CDC.
1958	A CDC team responds to epidemics of cholera and smallpox in Asia.
1960	The Tuberculosis Program is transferred to CDC.
1961	The *Morbidity and Mortality Weekly Report (MMWR)* is transferred to CDC from the National Office of Vital Statistics.
1963	The jet injection gun and vaccine for smallpox are tested at CDC.
1964	The US Surgeon General's report on smoking is released; a permanent Advisory Committee on Immunization Practices is appointed by the US Surgeon General.
1965	William Stewart (EIS 1951) is appointed US Surgeon General.
1966	The Global Smallpox Eradication Programs are initiated.
1967	The Congenital Malformations Unit is formed.
1969	CDC opens a biocontainment laboratory.
1970	The CDC name is changed to the Center for Disease Control.

Table continues

Appendix Table 1. Continued

Year	Key Event
1973	The National Institute for Occupational Safety and Health (NIOSH) becomes part of CDC (Ohio and West Virginia); on the basis of CDC research, the first Environmental Protection Agency standards are published to phase out lead in gasoline.
1974	CDC leads a major national immunization campaign.
1976	The National Influenza Immunization Program is established in response to swine flu.
1977	The last case of naturally acquired smallpox (variola minor) occurs; William H. Foege, MD (EIS 1962), is the first EIS alumnus to be named CDC director.
1978	The first outbreak of tuberculosis resistance to previously effective drugs occurs.
1980	The first Field Epidemiology Training Program (Thailand) is established.
1981	The first scientific publication of the human immunodeficiency virus pandemic appears in the *MMWR*, June 5; CDC is reorganized and renamed the Centers for Disease Control.
1982	CDC reports in *MMWR* the risk of Reye syndrome with use of aspirin among children with chickenpox or influenza.
1983	The violence epidemiology branch is established at CDC; James O. Mason (EIS 1959) is named CDC Director and Administrator of the newly created Agency for Toxic Substances and Disease Registry.
1986	The Office of Smoking and Health returns to CDC.
1987	The National Center for Health Statistics moves to CDC.
1992	CDC is renamed the Centers for Disease Control and Prevention.
1995	The federal building in Oklahoma City, Oklahoma, is bombed.
1996	Bombings occur at the Atlanta Summer Olympics and other sites.
1998	Jeffrey Koplan (EIS 1972) is named CDC Director.
2001	Year of the EIS 50th anniversary; terrorists attack New York City and Washington, DC, and anthrax-tainted letters are sent through the US Postal Service.
2003	Events include a global severe acute respiratory syndrome epidemic, a national monkeypox epidemic, and an electricity blackout in the northeastern United States.
2005	Hurricanes Katrina and Rita occur.
2009	Thomas R. Frieden (EIS 1990) is named CDC Director.