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Evolution of Epidemic Investigations and Field Epidemiology during the MMWR Era at CDC --- 1961--2011

Supplements

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Introduction

Since 1946, CDC has provided rapid assistance to states, federal agencies, international organizations, and ministries of health, often through formal requests for epidemic-assistance investigations (Epi-Aids) (*1*). The Epi-Aid mechanism provides CDC with the agility to respond rapidly to serious and urgent public health crises. Epi-Aids operationalize the tenets of field epidemiology and are used to provide information, as quickly as possible, on which the processes of selecting and implementing interventions can be based to lessen or prevent illness, injury, or death (*2,3*).

A total of 4,997 Epi-Aids have been conducted, of which 4,673 (94%) have occurred since 1960. Of the 556 international investigations, 551 (99%) have occurred since *MMWR* was transferred to CDC in 1960. Approximately 90% of these investigations have involved the approximately 3,000 Epidemic Intelligence Service officers (EISOs) who have trained at CDC since the program was initiated in 1951; however, only 218 EISOs came to CDC before *MMWR* arrived. EISOs assigned to state and local health departments conduct additional investigations within the states to which they are assigned. During the past 50 years, EISOs collectively have conducted approximately 5,000 state-based investigations without using the formal Epi-Aid request mechanism.

The goal of Epi-Aids is to control an epidemic and to prevent future epidemics attributable to the same or related causes. The specific objectives of an investigation are to define the parameters of the epidemic (i.e., time of illness onset and conclusion of the epidemic, number of cases, and morbidity and mortality), to identify control or prevention measures, and possibly to identify new data relative to the epidemiology of the health problem. Epi-Aids always are performed collaboratively with partners domestically or internationally.

Justification for investigating epidemics include

- increased disease or injury severity (e.g., its morbidity or mortality or other determinants of severity);
- occurrence of a rare or unknown disease or a change in the pattern of the disease's occurrence;
- opportunity to identify new information (e.g., risk factors previously unassociated with that disease or a change in transmission method);
- occurrence among a particular population (e.g., children or older persons);
- public or political concern;
- opportunity to conduct research on a specific disease; and
- opportunity to train personnel (e.g., EISOs or state and local field investigators) in the methodology of field investigations.

The 13 steps in an epidemic field investigation (Box) are adaptable to the circumstances of the problem, resources available, or cause or suspected cause of the disease. Altering the order of the steps might be necessary (e.g., possibly instituting control measures before completing data analyses), but all of the steps should be completed. These steps are as valid today as they were during the first field investigations over a half century ago, but the methodology of field investigations has evolved, as has the complexity of epidemics.

Four evolutionary changes throughout the past 50 years have resulted in more comprehensive investigations, as observed through *MMWR*. They include

- improved tools in science, technology, and communication;
- broader scope both in terms of geography and the nature of the public health problems under investigation;
- a better trained and equipped workforce that includes not only epidemiologists, public health advisors, microbiologists, and statisticians, but also behavioral and social scientists, economists, informaticians, toxicologists, and chemists; and
- new or changed roles for CDC's public health partners (e.g., U.S. Environmental Protection Agency, Department of Justice, Department of Housing and Urban Development, Department of Homeland Security, and Federal Bureau of Investigation and local law enforcement) and enhanced collaborations with the Indian Health Service; the U.S. Department of Agriculture; the Food and Drug Administration; the National Institutes of Health; the World Health Organization; and the private sector, including the business community, academia, community-based organizations, health plans, professional societies, volunteer agencies, and international organizations.

Before *MMWR* was transferred to CDC in 1960, most Epi-Aids were conducted in response to infectious agents, although environmental problems, including disasters, also were addressed. Subsequent years continued to include investigations of infectious disease epidemics but increasingly included environmental exposures, birth defects, genetic diseases, reproductive health, tobacco, cancer, unintentional injury, violence, legal debate, and terrorism. These Epi-Aids heralded expansion of CDC's mission and included new methods in statistics and applied epidemiology. Recommendations from these investigations have led to implementation, evaluation, or modification of public health policies. For example, during the 1970s, salmonellosis among children throughout the country was investigated, and the risk factor was contact with baby semi-aquatic turtles sold in pet stores. Subsequently, sale of these turtles was banned (*4*). During the 1990s, an epidemic of *Escherichia coli* O157:H7 diarrhea was investigated, and the risk factor was identified as eating undercooked hamburgers served at multiple fast-food outlets of one chain (*5*). A new policy of serving only well-cooked hamburgers was implemented.

The tools available to epidemiologists have evolved since 1961 and have been adapted to address whatever emergent health problems arise. Evolution of statistical methods in the acute setting of the Epi-Aid reflects a similar pattern in other public health disciplines (*6*). Especially notable are 1) the increased use of multivariate modeling beginning in the late 1970s, paralleling advances in computer hardware, especially the laptop, and 2) advances in computer software, most notably the CDC-sponsored Epi Info, an open-source software package developed in the 1980s for practicing epidemiologists and now translated into 14 languages (*7*).

Similarly, advances in laboratory practice have kept pace with the complexities of the investigations (*8*). For example, in 1961, the distance between the food source and the dinner table was considerably shorter than today, when a substantial amount of food is transported across the United States or imported from abroad. A public health official 50 years ago usually could not detect an outbreak until a substantial number of cases emerged in a single area or from a single event (e.g., a picnic or party). Today, in contrast, use of pulsed-field gel electrophoresis to create a DNA fingerprint enables associating a limited number of cases of a disease throughout a wide geographic area with a single common source. PulseNet, the laboratory-based foodborne diseases surveillance system, benefits not only from enhanced information science but also from increased diagnostic specificity (*9*). An example of the importance of this new technology was the epidemic of *Salmonella enterica* serotype Tennessee caused by contaminated peanut butter products in 2006--2007, with cases occurring in 47 states (*9,10*). DNA identification demonstrated that the cause of the epidemic was peanut butter from one factory, which when investigated, revealed multiple problems in its production process. Because the epidemiologic capacity of state and local health departments is higher now than in former years, for large outbreaks, CDC's role today often has become one of national coordination of multiple state-based investigations. EISOs in the field join with state and local colleagues to conduct parts of a larger nationwide investigation.

These advances, as well as others (e.g., geographic information systems), have enabled extraction of more data from field investigations and have increased the ability to determine the cause of an adverse health outcome. Descriptive epidemiology alone can help determine causation, but increasing knowledge of the multifactorial causes of disease has made involvement of the laboratorian and statistical analyses of the data of prime importance in deriving valid conclusions regarding cause and effect.

Steps in an Investigation

Despite the availability of new technology, what has not changed is the need for careful and thorough data collection and rigorous analysis of those data, thoughtful interpretation of the findings, and the willingness to continue to question the findings while confronted with the primary objective --- to control a problem quickly and effectively. The essential steps remain the same as in 1960.

When epidemiologists receive information about a possible epidemic, they should confirm its existence by comparing reported data with public health surveillance data collected during previous years (Box). If surveillance data for a particular disease or syndrome are unavailable, local health officials might be able to provide an informal assessment of past occurrence of the condition within their community. For many outbreaks, investigators can help confirm the diagnosis by submitting specimens for examination to a state or local laboratory, or sometimes to CDC. However, for some outbreaks, methods of confirmation are unavailable, and the investigation has to be initiated without confirmation of the diagnosis.

In planning participation in an investigation, the investigator must consider what materials should be taken into the field that will be unavailable locally. This might include specimen collection equipment; laboratory equipment; a calculator; a laptop computer; a generic or standardized questionnaire; reference material about the disease; and possibly, personal protective equipment. In 1961, neither the calculator nor the laptop was available. Specimen collection and laboratory equipment, as well as personal protective equipment, have changed dramatically, and today these tools often are available locally. Today, many investigations that would have resulted in an Epi-Aid request to CDC are handled locally, although still often reported in *MMWR* (*11*).

For Epi-Aids involving invited CDC staff, upon arriving at the scene of the epidemic, investigators meet with the local health authorities who requested assistance to discuss the information that has been developed locally. An immediate decision should be made regarding who will be in charge of the investigation and who will provide media reports. The investigators should, with appropriate permissions, examine selected patients to verify the diagnosis and develop a differential diagnosis of the cause of the outbreak. From the initial assessment of the clinical and epidemiologic information, a case definition should be established. Depending on the nature of the disease and the objectives of the investigation, the case definition should be either broad or narrow, which influences its sensitivity and specificity.

Data collected every day should be analyzed at the end of that day because identifying a control measure or measures before all cases have been recognized might be possible. Clearly this depends on the epidemic but is an important consideration in all investigations. For example, an epidemic of hepatitis A in Pascagoula, Mississippi, in 1961, might have disrupted production by a local company of atomic submarines for the U.S. Navy had it continued (*12*). Upon arrival in Pascagoula, by using a local directory, the investigating epidemiologist contacted patients by telephone. After completing interviews with selected patients, the epidemiologist contacted an equal number of controls. An analysis of these data at the end of the first day of the investigation strongly indicated that ingestion of raw shellfish was the risk factor involved. The epidemiologist was able to come to this conclusion before interviewing all of the patients. On the basis of these early findings, a decision was made to publicize the problem and to recommend that raw shellfish no longer be eaten. This action terminated the occurrence of new exposures; after completing interviews with all patients, the initial preliminary conclusion was confirmed.

Early in an investigation, categorizing cases as possible, probable, or confirmed on the basis of available data and knowledge is often necessary. An example of the importance of categorization occurred during the investigation of Legionnaires disease in Pennsylvania in 1976. The initial case definition required that patients had been in the main conference hotel. Illnesses of certain other patients met the clinical case definition except that they had not been in the hotel; thus their illnesses were put in a separate category called "Broad Street pneumonia." Later, after the etiologic agent was identified and a serologic test developed, the Broad Street pneumonia cases were recognized as cases of Legionnaires disease, just as the cases in the hotel. The Board Street pneumonia cases were included in the final tabulation for the outbreak.

The 1976 Legionnaires disease investigation also illustrates the key role of *MMWR* in keeping the medical and public health communities informed through updates in the weekly report. The first report was published less than a week after CDC was notified of the epidemic (*13*). Four more updates followed, with the last reporting identification of the bacterium that caused the disease (*14*) 11 months before publication in a peer-reviewed journal (*15*). This last report was also the first *MMWR* article published on a day other than Friday, highlighting the urgency in reporting the findings.

After all the patients have been interviewed during an investigation, the data should be oriented by time, place, and person. Then a hypothesis should be developed on the basis of the data that have been collected. It should be a unifying hypothesis (i.e., one risk factor related to the epidemic), recognizing that multiple risk factors might be involved. If uncertainty exists about the hypothesis, an analytic investigation (e.g., a case-control or cohort study) might be needed. After a hypothesis has been identified that fits the facts, corresponding control and prevention measures should be determined and implemented. Surveillance must be maintained to evaluate whether the hypothesis was correct and the control strategy is working. If the number of new cases decreases and the decrease is believed to result from the control measures, the investigation can be completed by writing and disseminating the final report. However, if cases continue to occur, the investigation has to be continued and different hypotheses tested. This happened during an outbreak of S. enterica serotype Saintpaul in 2008 in which approximately 1,400 persons in 43 states, the District of Columbia, and Canada were infected (*16*). Preliminary evidence implicated tomatoes as the transmission vehicle, but further epidemiologic and microbiologic investigations identified jalapeno and serrano peppers as the primary vehicles.

Recently epidemiologists have used the Internet as a tool for data collection, although the validity of that use remains under scrutiny. As noted elsewhere in this supplement (*17*), *MMWR* can reach tens of thousands of public health professionals in a very short time. The fact that the weekly edition can, in fact, be published electronically at any time, day or night, can facilitate case ascertainment in an ongoing investigation. Along with the effective outreach of *Epi-X* (a CDC-managed secure communications network for public health professionals) to public health partners, regional, national, and international case ascertainment is expanded (*18*). Meanwhile, the World-Wide Web has opened channels of communication that are more timely and far reaching than could have been imagined in 1961. Well-crafted, timely, and accurate updates of an investigation help the medical and public health communities, as well as the public, stay abreast of ongoing investigations, and they assist in implementing timely interventions to protect the public.

For CDC epidemiologists investigating outbreaks in the field, just as in 1960, writing a report is critically important. The report provides local public health departments an explanation of the parameters and the epidemic's cause, which enables timely and effective public health action. A secondary benefit of a report is its value as a useful training document for current staff and incoming epidemiologists. The report should identify the risk factors that resulted in the epidemic, and the report should be disseminated to the population involved in the epidemic to educate the public about control and prevention measures. Also, the report can be distributed to other public health professionals to help prevent a future similar problem.

The results of an investigation often indicate the need for other studies related to the disease or injury. For example, investigation of epidemics of Ebola virus hemorrhagic fever identified control measures (e.g., preventing contact with bloody secretions from patients or contaminated needles and syringes). What remains unknown and continues to be investigated is the reservoir for Ebola virus, which might be another mammal (e.g., primates) (*19*).

Future of Epidemic Investigations

New science and technology will continue to improve the epidemiologist's approach to outbreak investigation. Rapid technology development in the laboratory has improved diagnostic precision and reduced the time necessary to make a diagnosis. These improvements should continue, for example, to identify pathogens in imported foods at the place of importation and among persons who now travel more extensively and more rapidly around the globe. Similarly, increased use of electronic health records will facilitate more timely and accurate data collection as well as real-time dissemination of recommended control measures to clinicians and health-care facilities. Statisticians continue to develop new statistical methods that will provide insights through refined data analysis. For example, mathematical modeling, especially in complex and time-consuming investigations (e.g., pandemic influenza) can enable application of control measures to reduce the number of cases that are epidemic related. Improved techniques for training also need to be developed so that the technology of epidemic investigations can be used effectively by public health personnel both in the United States and internationally.

Alexander D. Langmuir, the man who brought *MMWR* to CDC in 1960, would be pleased with its first 50 years at CDC. It still often publishes the first scientific report of an unfolding epidemic investigation, and the reports continue through the different stages of the outbreak or incident. For example, on April 21, 2009, *MMWR* published a rapid report of the first cases of 2009 pandemic influenza A (H1N1) (*20*), and then published 45 articles on the virus and the pandemic in the subsequent several months, many reporting on ongoing investigations and others providing recommendations based on the findings of those investigations. Just as Langmuir envisioned, *MMWR* remains an important mechanism for reporting epidemic investigations in a timely and credible way.

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BOX. The 14 steps of an epidemic investigation

1. Confirm the existence of an epidemic.
2. Verify the diagnosis.
3. Develop a case definition.
4. Develop a case report form.
5. Count the cases (i.e., an approximate analysis).
6. Orient the data (i.e., time, place, and person).
7. Analyze the data (e.g., agent, transmission, and host).
8. Develop a hypothesis.
9. Test the hypothesis.
10. Plan and implement control and prevention measures.

11. Evaluate the implemented measures.
12. Establish or improve the public health surveillance.
13. Write a report.
14. Plan and conduct additional studies.

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