Serological Epidemiology

SEROLOGICAL EPIDEMIOLOGY

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Preface

The aim of this work is to give an overview of serological epidemiology for students of medicine and epidemiology and for research workers and health officers who either use serological techniques in the study of disease or are concerned with diseases in which these techniques have important application. The most common method of exposition used in the book is to outline the salient epidemiologic features of a specific disease and then to present the relevant immunological problems and findings. Some chapters, however, are concerned with a group of diseases and others are devoted to methodological issues or historical background.

In 1958 and again in 1969, the World Health Organization convened a committee of experts to report on multipurpose serological surveys. These meetings both stimulated and reflected an increasing interest in a new type of population survey in which the main feature is the collection of a sample of blood from each of the subjects included in the study. The principal objective in making these collections is to obtain data on the levels and patterns of antibodies in the serum and thus contribute to the epidemiology of infectious disease. However, the same collections may have secondary usefulness in population genetics, in nutrition, in hematology, and in the study of chronic diseases such as coronary heart disease.

Many of the serological techniques that are used in these studies have been introduced as tests for the diagnosis of individual patients. Their use in epidemiology requires an investigator to adopt a proper frame of reference for such research, namely, to define one or more target populations and to consider the adequacy of the sample that will be used to represent these populations. The occurrence of "fade-out" in measles among Island communities is a typical example of an interesting phenomenon in which the object of study is the population, not an individual or even a collection of individuals. Similarly, it is populations about which we make inferences when we study age-specific levels of poliomyelitis antibody in Cairo and Miami or of the rubella attack rate in those who have been vaccinated against the disease.

This is the first account, in book form, of Serological Epidemiology. We hope that it will provide an intellectual challenge by presenting certain phenomena of disease from a fresh point of view. It should also coordinate and consolidate our knowledge of the diseases involved and should point the way to programs of surveillance that will become increasingly important in the control of infectious disease.

The investigator who did most to develop serum surveys as an epidemiological method was the late John R. Paul. He coined the phrase "serological epidemiology." Dr. Paul exploited the potentiality of the method and helped establish serum banks that have facilitated the research of others in this field. He planned this book, and worked on it as editor until the time of his death. His colleagues affectionately dedicate it to his memory.

COLIN WHITE

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CHAPTER 1

Development and Use of Serum Surveys in Epidemiology

*JOHN R. PAUL**

In the 1920s and before, an apparently insoluble problem that confronted epidemiologists was a means of measuring degrees of susceptibility and resistance to disease in the human host. The usual way for the inquisitive physician to find out whether a given individual was either resistant or susceptible to measles or to chickenpox was by asking the patient or his parents whether he had experienced those common contagious diseases. To find out if an individual had been vaccinated against smallpox, a similar approach could be used, together with a search for a vaccination scar. Measuring immunity in the population as a whole was a different matter.

By the 1920s, however, advances had been made in testing immunity to some infections, and two tests, the Schick and, to a lesser extent, the tuberculin skin tests, were available. Here was a method at last of measuring man's immunity on an individual basis or on a large scale, even if it could be applied to only two diseases. Such skin test surveys measured tissue reactivity and indicated the presence of some degree of immunity based on previous infection with the causative agents. Frost's results, recording Schick tests in children of various age groups in New York City and Baltimore during the 1920s, were pioneer studies made when relatively few had been artificially immunized against diphtheria. They quickly brought to light the fact that age-specific patterns of immunity differed in different localities.

When serological tests entered the picture, naturally they were first used for diagnostic purposes on individual cases. One of the first of these to be employed on a mass basis was the Wassermann test for the diagnosis of syphilis. As early as 1916, Dr. J. Whitridge Williams of the Johns Hopkins Hospital had begun to require a routine Wassermann test† on all patients attending his prenatal clinic, a total averaging at that time well over 1000 per year (Williams, 1920). It was his purpose to map out the distribution of

*Author deceased.

†The Wassermann test for syphilis employs a nonspecific antigen which, if it reacts with the individual's serum, indicates the presence of this infection in its acute and subacute stages; a positive test is not necessarily an indication of immunity.

syphilis in segments of the urban population of Baltimore and bring under treatment those women who needed it, as well as to increase our "knowledge concerning the incidence of the disease." This was an extraordinary effort for its day.

Subsequently, the year 1930 saw the development of the neutralization test for the detection of poliovirus antibodies reach a point at which Aycock and Kramer felt they could use it to determine the immunity pattern of a given population for that infection (Aycock and Kramer, 1930). The claim was not made that immunity and the presence of antibody were one and the same, but, by and large, one reflected the other. Although the number of tests performed in monkeys lacked statistical adequacy, and the family of polioviruses had not yet been separated into its three component serotypes, Aycock and Kramer's results with this crude neutralization test marked a significant beginning. At the time, the authors hardly knew what an important step they had taken in the early application of serological methods for the study of epidemiology.

Some 20 years later, Aycock, in reviewing his most important contributions to epidemiology, published a small book for which he had set up the type and done the printing by hand (Aycock, 1949). In it he reproduced one of the charts from his earlier paper (Aycock and Kramer, 1930) comparing the way that poliovirus and diphtheria spread among the same two rural and urban populations (Fig. 1). The reasoning here was that spread of both infec-

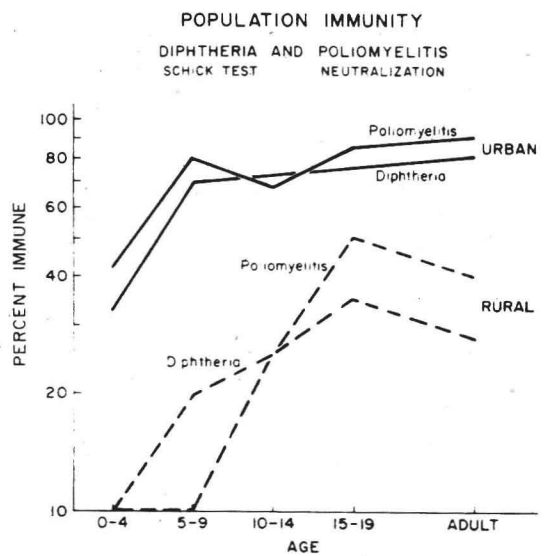

FIG. 1. Aycock and Kramer's prophetic chart. redrawn from an illustration which originally appeared in 1930.

tions was by close personal contact (the closer the better) through the medium of inapparent infections. The manner of dissemination was known for diphtheria, but only partially and imperfectly for poliomyelitis. Aycock and Kramer's study was a landmark in the history of serum surveys, and their interpretation of the differences in results in urban and rural populations has stood the test of time.

In the field of arboviruses, what may have been the earliest serological survey was conducted by Soper and his associates (1933) in Brazil. This was concerned with the prevalence of antibodies to yellow fever virus. The surveys in the vast jungle areas of Brazil were done under the auspices of the Rockefeller Foundation. From this work came the demonstration of the existence of jungle yellow fever. Subsequent surveys on a worldwide basis served to determine the distribution of yellow fever in Africa and in the Americas.

By the early 1940s, the use of serological screening of population groups had become a well-established technique for mapping the geographic distribution of another arbovirus infection, Japanese B encephalitis, both in man and animals (Tigertt and Hammon, 1950). It has subsequently been applied effectively in different parts of the world to document the occurrence of infections with dengue, St. Louis, western equine, and Russian spring-summer-Central European tickborne encephalitis (see Chapter 9 on arbovirus infections).

Serological surveys for influenza antibodies also date back to the mid-1930s. Swine influenza virus was first isolated in 1931, and human influenza in 1933. A neutralization test in ferrets and later in mice permitted differentiation of the two strains and the demonstration of antibody in animal and human sera. By 1935 a survey for swine and human influenza antibodies in different age groups in individuals from Great Britain, the United States, and Alaska was made by Andrewes *et al.* (1935) in England. Similar surveys were carried out at about the same time in the United States by Francis and Magill (1936), Shope (1936), and Brown (1936).

An interesting early application of serological epidemiology to the study of influenza was the examination of sera from persons living on the island of St. Helena, which had escaped the 1917–1921 pandemic. In 1938, Stuart-Harris *et al.* reported that during the course of a recent epidemic, residents of the island who were largely seronegative before the outbreak, developed antibodies to both human and swine strains. Seroconversions were detected in many who experienced no illness—one of the first demonstrations of *subclinical* influenza infection. The discovery in 1941 of hemagglutination by influenza viruses and of the hemagglutination-inhibition test (Hirst, 1941; McClelland and Hare, 1941) provided a strain-specific and simple method of antibody measurement. This test has been widely used in delineating the distribution of influenza antibodies in different populations, in defining the

relation of antibody level to immunity, and in the evaluation of vaccine effectiveness (see Chapter 7).

Thus beginning in the 1930s, the use of newly developed tools for determining immunity rapidly extended understanding of a number of infections. The subsequent application of serological epidemiology was perhaps most telling in the field of poliomyelitis in terms of elucidating the complex nature of the disease and its puzzling behavior in different populations. For this reason, the rest of this chapter will be devoted to a more detailed account of poliomyelitis as an example of how the potential of the serological approach was realized in solving difficult epidemiologic problems.

After 1935, serum surveys of different communities to detect poliovirus antibodies followed along the lines pursued by Aycock and Kramer (1930). One group made an attempt in 1935 to illustrate a crude pattern on an age-specific, worldwide base. The data were presented in the form of a graph (Fig. 2) and were derived from neutralization tests performed in monkeys by the Yale Poliomyelitis Study Unit and from results of other such tests collected from the literature (Paul and Trask, 1935). It was the first effort to compare human poliovirus antibody patterns in recent convalescents and in normals on a global basis—and not surprisingly it was the last.

The antibody curves shown in Fig. 2 demonstrated certain differences between the findings among those who had experienced the disease during the

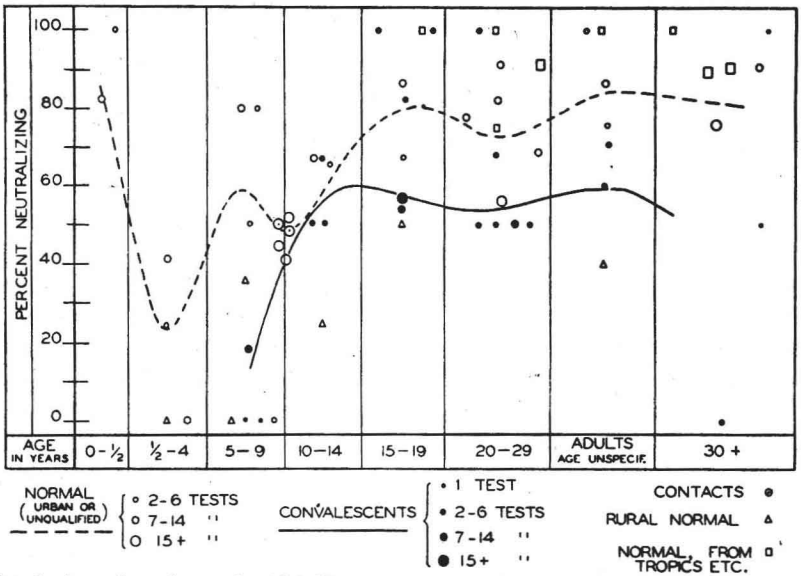

FIG. 2. A crude early graph which illustrates percent of convalescents and normals whose sera contained poliovirus antibodies, arranged according to age group. [Data from Paul and Trask 1935.]

epidemic of 1931 in the northeastern United States, and healthy normals of the same age groups, whose sera had been collected contemporaneously. Needless to say, these results were grossly inadequate. First of all, the data consisted of a hodgepodge, published some 15 years before the family of polioviruses was finally separated into its three component serotypes. But despite inadequacies, both immunological and statistical, the study revealed certain basic features which are familiar enough today. These included the demonstration that almost all infants are born with short-lived passive poliovirus antibodies derived from their mothers. Having lost these after about 6 or 7 months, a certain proportion began to acquire antibodies and *active* immunity the hard way—by specific infection. The percentage increased steadily until about the age of 15, when between 80 and 100% of children were antibody-positive. Also (see Fig. 2) the highest percentages with evidences of immunity, surprisingly, were recorded in normal adolescents and adults from tropical areas, where, according to some "authorities" in the 1920s and 1930s, poliomyelitis was not supposed to exist! Regardless of the crudity of this early attempt to measure immunity to poliomyelitis on a global scale, several unexpected features had come to the fore.

Up to the 1940s poliovirus-neutralizing antibody tests could be made only in monkeys—a method considered inaccurate by some (Schaeffer and Muckenfuss, 1940). Adaptation of poliovirus to rodents by Armstrong (1939) which led to the development of the mouse-neutralization test naturally came as an important advance. Although it measured antibody against only one type (Type II) represented by the Lansing strain (and no one knew in the early or mid 1940s, what proportion of clinical or inapparent human infections were due to Type II), the new test was a great contribution to the whole field of poliovirus research.

Hammon and Izumi (1942) were among the first to use this test as a type-specific *diagnostic* measure on human cases of poliomyelitis. Three years later, Turner *et al.* (1945) at the Johns Hopkins School of Hygiene took advantage of the mouse test to make a signal advance. They began with the concept that if enough serum samples were obtained from normal children, adolescents, and young adults within a given population from the east side of Baltimore, one of the city's less favored sections, the results of antibody tests could illustrate the patterns of immunity to the Lansing strain of poliovirus in that particular urban group. The age-specific curve constructed by Turner (Fig. 3) with its rising percentages of positives during childhood, more or less resembled the graph illustrated in Fig. 2, but it was a much more exact measure of immunity in that it was limited to a single type of poliovirus and to a single circumscribed population. In due time Turner's graph became a familiar pattern for urban communities in many parts of the world during the decade which preceded the vaccination era. Later it