Topley and Wilson's

Principles of bacteriology, virology and immunity

Seventh edition in four volumes

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Volume 3

Bacterial diseases

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General Editors' Preface to 7th edition

After the publication of the 6th edition in 1975 we had to decide whether it would be desirable to embark on a further edition and, if so, what form it should take. Except for the single-volume edition of 1936, the book had always appeared in two volumes. We hesitated to alter this arrangement but reflection made us realize that a change would be necessary.

If due attention was to be paid to the increase in knowledge that had occurred during the previous ten years two volumes would no longer be sufficient. Not only had the whole subject of microbiology expanded greatly, but some portions of it had assumed a disciplinary status of their own. Remembering always that our primary concern was with the causation and prevention of microbial disease, we had to select that part of the newer knowledge that was of sufficient relevance to be incorporated in the next edition without substantial enlargement of the book as a whole.

One of the subjects that demanded consideration was virology, which would have to be dealt with more fully than in the 6th edition. Another was immunology. Important as this subject is, much of it is not directly concerned with immunity to infectious disease. Moreover, numerous books, reviews and reports were readily available for the student to consult. What was required by the microbiologist and allied workers was a knowledge of serology, and by the medical and veterinary student a knowledge of the mechanisms by which the body defends itself against attack by bacteria and viruses. We resolved, therefore, to provide a plain straightforward account of these two aspects of immunity similar to but less detailed than that in the 6th edition.

The book we now present consists of four volumes. The first serves as a general introduction to bacteriology including an account of the morphology, physiology, and variability of bacteria, disinfection, antibiotic agents, bacterial genetics and bacteriophages, together with immunity to infections, ecology, the bacteriology of air, water, and milk, and the normal flora of the body. Volume 2 deals entirely with systematic bacteriology, volume 3 with bacterial disease, and volume 4 with virology.

To this last volume we would draw special attention. It contains 27 chapters describing the viruses in detail and the diseases in man and animals to which they give rise, and is a compendium of information suitable alike for the general reader and the specialist virologist.

The first two editions of this book were written by Topley and Wilson, and the third and fourth by Wilson and Miles. For the next two editions a few outside contributors were brought in to bridge the gap that neither of us could fill. For the present edition we enlisted a total of over fifty contributors. With their help every chapter in the book has been either rewritten or extensively revised. This has led to certain innovations. The author's name is given at the head of each chapter; and each chapter is prefaced by a detailed contents list so as to afford the reader a conspectus of the subject matter. This, in turn, has led to a shortening of the index, which is now used principally to show where subjects not obviously related to any particular chapter may be found. A separate but consequently shorter index is provided for each of the first three volumes and a cumulative index for all four volumes at the end of volume 4. Each volume will be on sale separately. As a result of these changes we shall no longer be able to ensure the uniformity of style and presentation for which we have always striven, or to take responsibility for the truth of every factual statement.

We are fortunate in having Dr Parker, who has been associated with the 5th and 6th editions of the book, as the third general editor of all four parts of this edition and as editor of volume 2. Dr Geoffrey Smith with his extensive knowledge of animal disease has greatly assisted us both as a contributor and as editor of volume 3. Dr Fred Brown, formerly of the Animal Virus Research Institute, Pirbright, has organized the production of volume 4, and Professor Heather Dick the immunity section of volume 1.

Two small technical matters may be mentioned. Firstly, in volume 2 we have retained many of the original photomicrographs and added others at similar magnifications because they portray what the student sees when he looks down an ordinary light microscope in the course of identifying bacteria. Electronmicrographs have been used mainly to illustrate general statements about the structure of the organisms under consideration. Secondly, all temperatures are given in degrees Celsius unless otherwise stated.

Apart from those to whom we have just expressed our thanks, and the authors and revisers of individual chapters, we are grateful to the numerous workers who have generously supplied us with illustrations; to Dr N. S. Galbraith and Mrs Hepner at Colindale for furnishing us with recent epidemiological information; to Dr Dorothy Jones at Leicester for advice on the *Corynebacterium* chapter and Dr Elizabeth Sharpe at Reading for information about *Lactobacillus*; to Dr R. Redfern at Tolworth for his opinion on the value of different rodent baits; to Mr C. J. Webb of the Visual Aids Department of the London School of Hygiene and Tropical Medicine for the reproduction of various photographs and diagrams; and finally to the Library staff at the London School and Miss Betty Whyte, until recently chief librarian of the Central Public Health Laboratory at Colindale, for the continuous and unstinted help they have given us in putting their bibliographical experience at our disposal.

GSW
AAM

Volume Editor's Preface

The infectious diseases—bacterial, mycoplasmal, chlamydial and rickettsial—that affect man and animals form the subject matter of Volume 3. Here is to be found the practical application of the detailed bacteriology in the preceding volume, with particular emphasis being placed on epidemiology, diagnosis, prophylaxis and control. Some sections, such as those on mycoplasmal, chlamydial, bacteroides, pasteurella and campylobacter infections, have been extensively re-written to take account of the rapidly expanding knowledge in human and animal disease, or of a greater veterinary importance than that reflected in earlier editions. The remainder have been carefully scrutinized, partly re-written, and brought up to date. The descriptions of 'new' diseases, such as enteritis in man due to *Yersinia enterocolitica*, *Clostridium difficile* or *Campylobacter*, Legionnaires' disease, infant botulism, and contagious equine metritis, are based on the vast literature that has already accumulated without being so lengthy as to destroy the balance of the book.

Particular attention has been paid to the so-called opportunist infections caused by organisms that were previously regarded as non-pathogenic but are now known to be responsible for much infection and cross-infection in hospitals. Again, an entirely new chapter has been devoted to the infections caused by the somewhat neglected group of anaerobic non-sporing gram-negative bacteria. Advances have been made in recent years in the method of cultivating these organisms, and as a result their isolation in the routine clinical laboratory is already more frequent than it has been in the past. Knowledge of the food-borne diseases has greatly increased of late years, requiring a fuller description of the part played not only by some of the organisms mentioned above, but also by the enterotoxic action of well known members of the food-poisoning group. A much needed chapter on epidemiology has been added to serve as a suitable introduction to the description of the various infectious diseases that follows. As in previous editions, due regard has been paid to the more important historical aspects of infectious disease, and certain sections describing early investigations have been retained because of their special interest or significance in medical and veterinary bacteriology.

For a description of the numerous infectious diseases caused by viruses, the reader is referred to Volume 4.

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General epidemiology

Graham Wilson

Introductory

Epidemiology is a subject covering a wide field without any natural boundaries. It has been defined in different terms by various workers according to the aspect on which, they consider, most emphasis should be laid (see Evans 1979). For practical purposes it deals with the nature, distribution, causation, mode of transfer, prevention, and control of disease. Though in the past it has been concerned with the study of infectious disease, it is now being increasingly applied to the non-communicable diseases, such as diabetes, coronary occlusion, nutritive disorders, cancer, industrial and road accidents, and even to health (see Morris 1975). Both for information and technique it draws on the biological, social and mathematical sciences (Rojas 1964).

Epidemiology is the counterpart of clinical medicine, taking the population group or herd as the unit of study rather than the individual patient. The clinician observes differences between the patient and healthy persons of similar age and sex: the epidemiologist compares the occurrence of disease in the population group in question with that in other groups differing in various respects—race, climate, diet, occupation, and general environment. The clinician deals with absolute numbers, the epidemiologist with rates—prevalence, incidence, morbidity, mortality and so on—expressed as ratios of cases to the population.

The functions of the epidemiologist in relation to infectious diseases are to determine the rates, and in this way to act as a bureau of information to be drawn upon by students and administrators of community medicine; to investigate outbreaks of disease, their cause, source, reservoirs, mode of transfer, attack and mortality rates; to make *ad hoc* inquiries into the occurrence of the less common diseases; to devise and institute surveillance programmes, usually by field studies in order to ascertain the prevalence of selected diseases and the effect that control measures, if any, are having on them; to consider the means of preventing future outbreaks and of controlling existing outbreaks; and to carry out controlled trials of vaccines or drugs. The information on which rates are determined and calculated often requires analysis by statistical methods; and investigation, surveillance and vaccination programmes demand the cooperation of the microbiologist.

For descriptive purposes it is convenient to divide epidemiology into two types: investigational and administrative, distinguished by the nature of the problems concerned and the approach to them. The **investigational epidemiologist** makes observations either on naturally occurring phenomena, or on controlled phenomena experimentally produced. Thus, he may observe that anthrax in cattle in Southern Europe and the Middle East is an epidemic disease occurring in the summer months, whereas in Northern Europe it is a sporadic disease occurring in the winter months; or that the virus of foot-and-mouth disease can infect at a distance, whereas that of the clinically almost indistinguishable vesicular disease of swine requires close contact between infected animals; or that the mode of infection with tularaemia or Q fever varies from country to country. In such instances his task is to try and find out the cause of these disparities, explaining them in scientifically acceptable terms. Occasionally, when the natural phenomena are too complex, he may resort to the experimental method to test a particular hypothesis. For example, he may devise methods to decide whether bubonic plague in rats is spread by fleas or by some other means; or whether infection in yellow fever in man is spread by air, or mosquitoes; or babesiosis in cattle by contagion or by ticks. Whether engaged in natural or experimental inquiry the investigational epidemiologist should ideally be located in a microbiological laboratory where he can obtain first-hand information on the presence and distribution of pathogenic organisms in the locality and, when necessary, their phage, sero, or bacteriocine type. The staff of the microbiological laboratory can also be of help in participating in the field inquiries that are so often called for, taking specimens and examining them promptly under the most suitable conditions.

The **administrative epidemiologist**, on the other hand, should be located in a Ministry, Department, or other governmental body that deals primarily with the health of the nation. His task is to collect and analyse all the information he can get, much of it coming from hospital and microbiological laboratories throughout the country, some of it supplied by the police, newspapers, veterinary workers, or other sources. From this information, but chiefly from returns of births and deaths received by a central office, he works out rates of various sorts so as to enable him to determine what priority to give to preventive or control measures, such as those for combating particular diseases, for cutting down infant or perinatal mortality, for improving the nutritional state of certain classes of the population, for instituting vaccination programmes, and for the welfare of the community as a whole. He is concerned not only with legislative practice at home, but with quarantine diseases on an international scale, supplying regular information to the World Health Organization. Together with his agricultural colleagues he must impose restrictions on the importation of contaminated food or raw materials, and keep an eye on the diseases brought into the country by immigrants or animals.

The investigational epidemiologist is essentially a field worker. He needs to have a good background of clinical experience, since the probable nature of a disease must often be recognized before the microbiologist knows what specimens to take and what tests to carry out on them. He should have spent some time in the study of community medicine and its impact on society, and should have a general knowledge of scientific methods, and, above all, a lively curiosity and imagination.

In contrast, the administrative epidemiologist is an office worker. If not medically qualified, he must be familiar with problems of health and disease. He needs to make use of the simpler statistical methods, to understand the working of the legislative machinery, to have a well balanced mind so as to be able to offer sound practical advice to the Government on the nature and priority of the measures to be taken, bearing in mind the probable behaviour and reaction of the people. Finally, he must keep under review both the infectious and the non-infectious diseases, the latter of which, by virtue of their frequent chronicity and the invalidity they cause, are in the more developed countries with ageing populations assuming increasing importance.

Analysis of observations

In studying the epidemiology of any infectious disease one has to take into account (a) the prime causative agent or parasite and its habitat; (b) the mode of transmission of the agent from its habitat or reservoir to the human or animal subject; and (c) the susceptibility of the subject and the various factors that contribute towards it.

Identification of the causative agent is generally the task of the microbiologist, but identification of its habitat or reservoir requires a combination of microbiologist and epidemiologist. Habitat and reservoir are not necessarily the same. The anthrax bacillus has its habitat or source in the soil, but man becomes infected indirectly from animals, which constitute for him the reservoir of infection.

The mode of transmission of the infective agent is not always easy to determine. For example, nearly 20 years elapsed between the discovery of the organism of Malta fever and the finding that it was carried by goats' milk. Incidentally, this illustrates the fact that in the prevention or control of a disease knowledge of the way in which it is spread is often of greater value than knowledge of the causative agent itself. The discovery of *Brucella melitensis* had no effect on the incidence of the disease in the military and naval forces in Malta; stoppage of goats' milk in their diet brought it immediately to an end. In tracing the pathway of spread by air, water, milk, food, direct contact, insect vector or other ways the epidemiologist and microbiologist should work hand in hand (see Wilson 1974).

Study of the third component, that is the degree of susceptibility of the subject exposed to the risk of infection and the factors affecting it, is one of the most complex tasks in epidemiology. The cause of a disease is always multifactorial. The parasite cannot cause disease unless it is brought into contact in sufficient numbers at a sufficient rate (velocity of infection) not only with the subject but with the appropriate receptive system of that subject, and unless the subject is susceptible to the particular infection concerned. Numerous predisposing factors influence both the transmission of the agent and the susceptibility of the subject, rendering it no easy task for the epidemiologist and statistician to decide which are the main determining ones. The ideal, of course, is to compare two populations as alike as possible in their age and sex distribution, their customs and mode of life, their diet, their socio-economic level, and every other respect except one, so that the presumption is that any difference noted between them in the incidence of disease is dependent on the one respect in which they differ. Under natural conditions this is usually impossible, but experimentally, as for example in trials of vaccines, a close approximation to it can often be attained. It cannot be emphasized too strongly that, wherever many factors are concerned in the causation of disease, great caution must be exercised before concluding that any single one of them is mainly responsible. In Denmark, for instance, when BCG vaccination of children was extensively used, the death rate from tuberculosis fell from 174 per 100 000 in 1918 to 16 per 100 000 in 1950. In Iceland, where BCG was not used, it fell from 189 per 100 000 in 1918 to 20 per 100 000 in 1950. In the absence of the figures from Iceland the temptation to conclude that BCG was responsible for the enormous decline in the tuberculosis death rate in Denmark would have been very strong (see Sigurdsson and Edwards 1952). Potential fallacies are numerous. The obvious cause is not necessarily the correct one. For example, the close association of paratyphoid fever with the eating of cream buns seemed to leave no doubt that the synthetic cream used was responsible for the infection. Investigation, however, showed that the synthetic cream, as it came from the factories, was almost sterile, but that on the baker's premises it became contaminated with processed egg containing *Salmonella paratyphi*. The real source of the infection was the egg; the synthetic cream acted merely as a passive vehicle. Or again, in diseases such as scarlet fever and diphtheria in which infection usually occurs by the respiratory route, the possibility of infection by some unusual route may be overlooked. In an outbreak of scarlet fever in Copenhagen in 1935, for example, where there were 10 000 cases, the milk-borne nature of the infection was not realized for three weeks.

When an association between a disease and some factor is judged to be real, Austin and Werner (1974) suggest the use of five criteria in helping to decide whether the factor causes the disease, the disease causes the factor, or another factor causes both: (a) consistency of the association; (b) strength of the association; (c) specificity of the association; (d) temporal relation of the factor to the association; (e) coherence of the association with other knowledge.

In the causation of a particular disease two main factors may apparently be playing a part; which of these so-called confounding variables (Austin and Werner 1974) is the more important may be determined by the method of cross-classification. In the causation of cervical cancer, for example, both age and parity are concerned, as is shown in Table 48.1.

Table 48.1 The risk of cervical cancer according to age and parity

No. of pregnancies	Age group in years 13–34	35–54	55+	All ages
1–2	2	3	4	3
3–5	5	6	7	6
6+	8	9	10	9
All	5	6	7	6

After Austin and Werner (1974).

In each age category it will be seen that the rates increase with parity; and that in every parity group the rates increase with age. Both factors are operative, but parity has the stronger effect.

When only two divisions of a factor are examined, such as 'with' and 'without', a simple 2 × 2 or fourfold contingency table may be used. The table has four

Table 48.2 The risk of dying within six years, in men aged 60–64, according to smoking habits

	Non-smokers	Pipe smokers	Total
Dead	117	54	171
Alive	950	348	1298
Total	1067	402	1469
Per cent dead	11.0	13.4	

After Snedecor and Cochran (1967).

cells, and the numbers go inside these and not in the margin (Table 48.2). The difference between non-smokers and pipe smokers is 2.4 per cent. Whether this is attributable to a sampling error or to a real difference in the death-rates of the two groups must then be determined by the usual tests for significance.

Investigation of outbreaks

The distribution between an *outbreak* and an *epidemic* is one of degree rather than of kind. An outbreak tends to be localized to a small area, or confined to a particular group of persons such as schoolchildren, diners at a restaurant or on a train, or participants at a conference coming from a distance. An epidemic, on the other hand, spreads over a wide area, such as a county, a region, the whole country, or as a pandemic over several countries.

In the investigation of an outbreak the aim of the epidemiologist must be to establish as far as possible the nature, distribution, causation, and mode of spread of the disease in question. He will ascertain the number of cases, the size of the population at risk, and, if there are any deaths, the case-fatality rate. He will study all likely causative factors, and will call on the microbiologist in the public health laboratory or in the regional veterinary laboratory to help him in establishing the agent responsible and its mode of transfer. Though there are many hundreds of parasitic agents, the body has only a few methods of response, so that without laboratory investigation it is often impossible to tell which organism is concerned. Moreover, for tracing the source of the organism, bacterial finger-printing by serological, bacteriophage, or bacteriocine methods may be essential. Serotyping, for instance, played an important part in the incrimination of spray-dried egg as a cause of food poisoning during the second world war (see Report 1947).

In 1941 and again in 1942 scattered cases of **typhoid fever** were observed in the **Home Counties** of England. The probability that they were infected from the same source was confirmed by finding that the organisms isolated from them all belonged to phage type D4—an uncommon type in the country. This led to the incrimination of milk coming from a wholesaler, one of whose suppliers was a farmer in the West of England who was found to be a chronic typhoid carrier (Bradley 1943).

Phage-typing likewise played a crucial part in the outbreak of typhoid fever among the nurses in the Orthopaedic Hospital at **Oswestry** in 1948 (Bradley *et al.* 1951). The epidemiological evidence pointed strongly to a milk-borne infection. This was strengthened by finding that the stream which was used for watering the cows and washing the milk churns on one of the farms was contaminated with the faecal discharge of a typhoid carrier. The conclusion that milk was acting as the vehicle of infection appeared on epidemiological grounds to be justified. This conclusion, however, was shown to be erroneous when it was found that the phage type of the typhoid bacillus isolated from the carrier was different from that isolated from the patients. It may be added that this outbreak, whose cause at the time was a mystery, had an extraordinary sequel. Some years later typhoid cases caused by the same Vi-phage type as that infecting the Oswestry nurses cropped up in various parts of the country. Investigation showed that they had followed the consumption of canned meat coming from a processing plant in the Argentine. At this plant the chlorination system for disinfecting the water used for cooling the autoclaved cans had been out of action for some time, with the consequence that the raw heavily contaminated water from the river had been used untreated. The strains of typhoid bacillus isolated from the patients (type 34) proved to be of the same phage type as those from the Oswestry nurses, suggesting that the nurses had probably been infected not from milk but from canned meat. Examination of the diet sheets confirmed this suspicion, showing that canned meat had in fact been served to the nurses on the particular day on which infection had apparently occurred (Anderson and Hobbs 1973).

Surveillance

The term surveillance has almost as many definitions as that of epidemiology. Literally it means to watch over. In practice, the watch is kept over diseases not over individuals. Its purpose is to keep track of (a) their prevalence; (b) changes in their distribution according to incidence, clinical form, mortality, age, sex, place, season, or other variable; and (c) their response to such preventive and control measures as are being taken. The ultimate aim, of course, is eradication or, where this is impracticable, reduction of their incidence to as low a level as possible. Surveillance may be carried out on a regional, national, or even international scale, and is usually a long-term project. Short-term surveillance, however, on a limited scale may be necessary when a disease is introduced into a country that is normally free of it; in such instances watch will be continued till no further cases occur and the disease has been eliminated. This was the practice with smallpox.

Again, short-term surveillance is recommended of children who have been exposed to common infectious diseases, such as measles, rubella, varicella and mumps. Contacts need not be kept away from school so long as there is a close watch over them, and they are isolated as soon as they show symptoms of the disease or reach the infectious stage (see Illingworth 1967; Raška 1983).

Acute diseases

Numerous special uses of surveillance may be mentioned. One of the most important is to be on the look-out for other diseases closely simulating the one that is being studied. Raška (1964), for example, refers to the confusion between pertussis and parapertussis. Though these two diseases resemble each other clinically, they differ in their epidemiology and in their prevention. Pulmonary disease caused by the tuberculoid group of mycobacteria may easily be mistaken for tuberculosis; and vesicular disease of swine for foot-and-mouth disease.

In a country with a well developed public health laboratory service the infectious diseases should be kept under such close supervision that no new disease could be introduced without its being rapidly detected. This, of course, implies the cooperation of district and regional health officers with a good system of notification and intercommunication.

Serological epidemiology

A useful method of surveillance consists in the routine collection of sera from patients suffering from what is or appears to be a new disease. These sera should be stored at $-70°C$. When, perhaps some years later, the disease occurs again, the patient's serum may be compared with the stored serum, and the identity of the new disease with that of the previous disease may be established.

A striking instance of this is afforded by the history of **influenza**. In 1957 a worldwide epidemic occurred caused by a new virus referred to as the Asian influenza virus. How this had arisen was a matter of conjecture. Examination, however, of a large number of sera from persons of different ages revealed the presence in elderly persons who had passed through the 1890–92 epidemic of antibodies to the haemagglutination-inhibiting (HI) antigen of the Asian strain. Apparently this antigen had formed part of the virus responsible for the 1890–92 epidemic and had lain dormant in man or taken refuge in an animal to reappear nearly 70 years later (see Masurel 1969; also Stuart-Harris and Schild 1976).

Another instance is that of **Legionnaires' disease** which occurred in outbreak form at a conference in Philadelphia in 1976. This was thought to be a new disease (see Chapter 73), but the examination of sera taken some years previously showed the presence of antibodies to the causative organism, indicating that the disease had occurred before but had not been recognized.

Stored sera are also of value in detecting the presence of infection when only subclinical cases are occurring.

Surveillance is likewise of value in a disease such as **influenza**, the causative virus of which is subject to varietal changes. By following the distribution, it may be possible to detect the advance of a particular pathogenic variety from one part of the world to another; and, with a knowledge of the previous exposure of the population to this or to a closely similar variety and the consequent immunological response, to forecast an epidemic of the disease and, if time allows, to prepare a suitable vaccine against it.

Apart from actual disease, a new vehicle carrying pathogenic microorganisms may be imported into the country. A notable example of this occurred during the second world war with the introduction from America of spray-dried egg containing various organisms of the *Salmonella* group. Such a mishap was not unexpected, since chickens were known to be the biggest reservoir of salmonella infection, and the temperature to which spray-dried egg was subjected during production was believed to be insufficient to destroy all vegetative organisms. This expectation soon proved to be correct. As the first shipment arrived at Liverpool, samples of the egg were distributed to a number of laboratories and were found to contain salmonellae. In spite of precautionary measures that were taken, cases of food poisoning occurred in the population; and the fact that these were caused not by indigenous strains of the organism but by strains that had not previously been met with in the country left no doubt that the egg was responsible.

Continued surveillance of patients who are convalescing or have recovered from a particular disease may bring to light complications whose connection with the disease might not otherwise have been suspected. Cirrhosis of the liver, for instance, may be a late complication of hepatitis. The occurrence of multiple cases of hepatitis B may be related to blood transfusion 3–5 months previously. Clinical observation alone may reveal the not infrequent occurrence of rheumatic fever after a streptococcal infection; but surveillance of large numbers of children suffering from various forms of streptococcal disease are necessary to ascertain the proportion that suffer from this complication, and to decide whether it is large enough to justify the use of penicillin as a routine prophylactic agent.

The frequency with which drug resistance is acquired in the treatment of various diseases is likewise