CHAPTER 1

Epidemiological Concepts

Alfred S. Evans[1]

1. Introduction

Epidemiology is the study of the distribution and determinants of health-related states, conditions, or events in specified populations and the application of the results of this study to the control of health problems.[1] It is a quantitative science concerned in infectious diseases with the circumstances under which disease processes occur, the factors that affect their incidence and the host response to the infectious agent, and the use of this knowledge for control and prevention.[2] It includes the pathogenesis of disease in both the community and the individual. For infectious diseases, one must study the circumstances under which both *infection* and *disease* occur, for these may be different. Infection is the consequence of an encounter of a potentially pathogenic microorganism with a susceptible human host through an appropriate portal of entry and usually involves a demonstrable host response to the agent. Exposure is the key factor, and the sources of infection lie mostly outside the individual human host, within the environment, or in other infected hosts. Disease represents one of the possible consequences of infection, and the factors important in its development are mostly intrinsic to the host, although the dosage and virulence of the infecting microbe play a role. These intrinsic factors include the age at the time of infection, the portal of entry, the presence or absence of immunity, the vigor of the primary defense system, the efficiency and nature of humoral and cell-mediated immune responses, the genetic makeup of the host, the state of nutrition, the presence of other diseases, and psychosocial influences. These factors that result in the occurrence of clinical illness among those infected have been called the "clinical illness-promotion factors,"[3] and many of them remain unknown. The host responses can include death, the classic clinical features of the disease, mild or atypical forms, subclinical and inapparent infections, and the carrier state, which may exist in the absence of a detectable host response. While the clinician is primarily concerned with disease, the epidemiologist is interested in both infection and disease. Infection without disease is a common phenomenon, so that a study limited to clinical illness alone would give an incomplete epidemiological picture and would be a poor basis for control and prevention.[4] A full understanding involves the pathogenesis of the process leading to clinical disease both in the community and in the individual.

The concepts of epidemiology in bacterial infections are very similar to those of viral infections as expounded in the companion volume, *Viral Infections of Humans*,[5] so there will be overlap and repetition in this volume. Some of the differences between viral and bacterial infection include the intracellular position of all viruses, their smaller size, the requirement of living tissues for viral multiplication, the ease with which many viruses are spread by respiratory routes or by insect vectors, the relatively high order of immunity following viral infection, the usefulness of serological tests for the diagnosis of most viral infections, and the failure of viral infections to respond to antibiotic therapy. Highly sensitive and specific molecular methods are being increasingly employed to define the agent and the host response to it.[6–8]

Many concepts and methods of epidemiology apply to both infectious and noninfectious diseases, and there should be no essential dichotomy between the two.[9] In general, epidemiology can be regarded as the development, pathogenesis, and expression of infection and disease in a community in much the same way as clinical

Alfred S. Evans • Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut 06510, USA (†Deceased).

It should be noted that this chapter is the original introductory chapter as written by Alfred S. Evans for the first edition in 1982.

[1]Deceased. Dr. D. Scott Schmid, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, assisted in revising Section 10, Immune Response, after Dr. Evans' death.

A.S. Evans, P.S. Brachman (eds.), *Bacterial Infections of Humans*, DOI 10.1007/978-0-387-09843-2_1,

medicine is concerned with the development, pathogenesis, and expression in the individual. This book will attempt to cover both these aspects. While the "epidemiology of infectious diseases" has disappeared from the curriculum of many schools of medicine and public health in developed countries, the current epidemic of the acquired immunodeficiency syndrome (AIDS) has reawakened interest in the subject. In addition, the emergence of new diseases such as Legionnaires' disease, Lyme disease, the toxic shock syndrome and the development of antibiotic-resistant pneumococci and tubercle bacilli, the appearance of erythrogenic streptococci ("flesh-eating" streptococci) and a new cholera strain termed 0139, foodborne outbreaks of *Escherichia coli* O157:H7, and a large waterborne outbreak of cryptosporidiosis are among the "emerging infections" that continue to pose challenges to epidemiologists[10] and for which the Centers for Disease Control and Prevention (CDC) are developing preventive strategies.[11] It is becoming apparent that in developed countries, the continuing, and in some instances the increasing, importance of infectious diseases is causing concern among public health authorities.

In developing countries, infectious diseases are still a major cause of morbidity and mortality, and efforts are in progress to develop training programs in epidemiology and in surveillance in such areas. The Field Epidemiology Training Program of the CDC is a fine example of this effort. Several recent texts address the problems of surveillance.[12–16]

2. Definitions and Methods

2.1. Definitions

A working understanding of the terms commonly used in epidemiology and infectious diseases may be helpful to the student, microbiologist, and clinician unfamiliar with them. They are derived from those in *A Dictionary of Epidemiology*,[1] *Viral Infections of Humans*,[5] and the American Public Health Association handbook entitled *Control of Communicable Diseases Manual*.[17]

Attack rate or case ratio: This ratio expresses incidence rates in population groups during specified time periods or under special circumstances such as in an epidemic. It is often expressed as a percent (cases per 100). The *secondary attack rate* is the proportion of persons who develop infection within an appropriate incubation period after exposure to a primary case divided by the number exposed. The groups so exposed are frequently family members or persons located in an institution.

Carrier: A carrier is a person, animal, or arthropod who harbors a specific infectious agent in the absence of clinical illness with or without a detectable immune response. The carrier state may reflect carriage of the organism in the incubation period before clinical symptoms appear, during an apparent or inapparent infection (healthy or asymptomatic carrier), or following recovery from illness; it may be of short or long duration (chronic carrier), and it may be intermittent or continuous. Carriers may spread the infectious agent to others.

Case-fatality rate: Number of deaths of a specific disease divided by the number of cases $\times$ 100.

Cell-mediated immunity: This term has been used previously to designate immune mechanisms largely dependent on lymphocyte activity and in contrast to "humoral immunity." As T lymphocytes are now recognized as playing an important role in both, the term *T-cell immunity* is being more widely used.

Chemoprophylaxis: Administration of a chemical or antibiotic to prevent infection or to prevent the development of disease in a person already infected.

Colonization: Multiplication of an organism on a body surface (e.g., skin, epithelium, mucus membrane) without evoking a tissue or immune response.

Communicable period: Time during which a person (or animal) is infectious for another person, animal, or arthropod.

Endemic: This term denotes the constant or usual presence of an infection or disease in a community. A high degree of endemicity is termed *hyperendemic*, and one with a particularly high level of infection beginning early in life and affecting most of the population is called *holoendemic*.

Epidemic: An epidemic or outbreak is said to exist when an unusual number of cases of a disease occur in a given time period and geographic area as compared with the previous experience with that disease in that area. For diseases already present in the community, it is necessary to know the number of existing cases (prevalence) as well as new cases (incidence) to determine whether an increase has occurred. The definition of increases or excess cases is arbitrary and will vary from disease to disease. See Section 3 for further discussion.

Host: A person, animal (including birds), or arthropod in which infectious agents subsist or infect under natural conditions. In this book the term will most often refer to the "human host" unless otherwise stated.

Immunity: The specific resistance to an infectious agent resulting from humoral and local antibodies and from cell-mediated responses constitutes immunity. Immunity may be acquired through natural infection, by active immunization, by transfer of immune factors via the placenta, or by passive immunization with antibodies from another person or animal. The immune state is relative and not absolute, is gov-

erned largely through genetic control, and may be altered by disease- or drug-induced immunosuppression.

Immunodeficiency: A state representing impairment of the immune system of the host that affects its ability to respond to a foreign antigen. This may result from an inherited defect, or an acquired one such as a result of the disease itself, or of immunosuppressive drugs or an infectious agent that depresses the immune system. The human immunodeficiency viruses (HIV-1 and HIV-2) are the major examples of the latter.

Incidence rate: The number of new events (specific infection or disease) occurring in a given time period in a given population as the numerator and the number of susceptible persons in that population exposed to the agent as the denominator. This is usually stated as cases (or infections) per 100, 1,000, or 100,000. This rate may be adjusted for an age- or sex-specific numerator and denominator or any other characteristic of interest. Laboratory procedures may be required for numerator data on new infections, as measured by isolation of the agent or by antibody rises, or by both. They may also be required to identify those actually at risk in the denominator, i.e., those lacking antibody; other means of refining the denominator would be by eliminating adults in calculating rates of childhood diseases or eliminating those with a valid history of having had the disease.

Incubation period: The incubation period is the interval between exposure and the appearance of the first detectable sign or symptom of the illness. Ill-defined exposure to a source of infection or exposure to persons without apparent illness may obscure the starting point of the incubation period, and vague, premonitory, or prodromal signs of illness may obscure its termination point. The best estimate is often derived from single exposures of short duration to a clinical case or established source of infection (e.g., air, food, water, arthropod vector) and the development of the first characteristic or classic features of the disease. Experimental infections in volunteers give well-defined incubation periods, but these may not always be the same as under natural conditions. See Section 7 for further discussion.

Index case: This is the index or primary case of an illness in a family, group, institution, or community that may serve as a source of infection to others.

Infection: Infection represents the deposition, colonization, and multiplication of a microorganism in a host and is usually accompanied by an immune response. Infection may occur with or without clinical illness.

Isolation: This is a term applied to the separation of infected persons in such places and/or under such conditions as to prevent contact or airborne transmission of the infectious agent to others during the period of communicability. Infection control practice in hospitals as recommended by the CDC has divided isolation into two tiers of isolation precautions. The first tier is known as *standard precautions* and the second tier *transmission-based precautions*. Hand washing remains a prime preventive measure in regard to nosocomial infections.

Morbidity rate: An incidence rate in which the numerator includes all persons clinically ill in a defined time and population and the denominator is the population involved or a subunit thereof, usually expressed as the number of cases per 100,000 persons at risk.

Mortality rate: The same as morbidity rate except the numerator consists of deaths. This may be the total number of deaths in a population group (crude mortality rate, usually expressed as deaths per 1,000) or deaths from a specific disease (disease-specific mortality, usually expressed as deaths per 100,000).

Nosocomial infections: This term refers to infections that develop after entry into a hospital or other health care institutions and that are not present or incubating at the time of admission or the residual of an infection acquired during a previous admission.

Pathogenicity: The ability of an infectious agent to produce disease in a susceptible host. Some nonpathogenic agents can become pathogenic in an immunocompromised host such as persons infected with HIV.

Prevalence rate: The ratio of the number of persons in a defined population who are affected with the disease at any one time as the numerator and the exposed population at that point as the denominator. If this is based on the frequency of cases at a moment in time, then the term *point prevalence* is used. If it reflects the proportion of persons affected over a longer period, then the term *period prevalence* is employed. Most infectious diseases are acute and short lived, so that prevalence rates are not commonly used. The use of prevalence rates is more relevant to more protracted illnesses such as subacute bacterial endocarditis, tuberculosis, and leprosy, or to reflect carrier states that may persist for months or years. Prevalence rates reflect incidence times duration of disease. In seroepidemiological usage, the term *prevalence* denotes the presence of antigen, antibody, or another component in the blood.

Quarantine: The restriction of persons or animals exposed to an infected source during the incubation period for that disease to observe if the disease develops in order that other persons will not be exposed to the infectious agent during that period.

Reservoir: A person, animal, soil, or other environment in which an infectious agent normally exists and multiplies and which can be a source of infection to other hosts.

Surveillance: As concerns public health, surveillance is the systematic collection of data pertaining to the occur-

rences of specific diseases or health-related conditions, the analysis and interpretation of these data, and the dissemination of consolidated and processed information to contributors to the program and other interested persons for purposes of control and/or prevention (see Chapter 2 for detailed discussion and Cutts et al.[12] for a World Health Organization definition, as used in the Expanded Programme in Immunization). *Serological surveillance* is the identification of current and past infection through measurement of antibody or of antigen in serum from representative samples of the population or other target groups.

Susceptibility: A state in which a person or animal is capable of being infected with a microorganism. The lack of specific protective antibody usually indicates susceptibility to that agent, although reactivation or reinfection to some agents may occur in the presence of antibody.

Transmission: The mechanism by which an infectious agent is spread to another host (see Section 5).

Virulence: A measure of the degree of pathogenicity of an infectious agent as reflected by the severity of the disease produced and its ability to invade the tissues of the host.

Zoonosis: An infection or infectious disease transmissible under natural conditions from animals to man. It may be *endemic* (enzootic) or *epidemic* (epizootic).

2.2. Methods

Epidemiology can be divided into descriptive, analytical, experimental, and serological epidemiology. The major analytic methods in use are the cohort (prospective) and case–control (retrospective). This section will briefly present these concepts. For more detailed descriptions, textbooks and recent articles of epidemiology are recommended.[18–21] A textbook on epidemiological methods that includes discussion and examples in infectious disease[18] is recommended before undertaking an epidemiological study. An excellent brief book on all aspects of epidemiological studies has been published by the World Health Organization (WHO).[22]

2.2.1. Types of Epidemiological Studies. Epidemiological studies may be descriptive or analytical. Descriptive studies are based on available data sources and describe the patterns of disease in population groups according to time, place, and person factors. Epidemic investigations begin with a descriptive study. These data often suggest clues to the etiology of the condition or to the risk factors involved. Analytical studies are then designed to test the hypotheses of causation developed from the descriptive studies and usually require new data to do so. Three common analytical methods are employed in pursuing epidemiological studies.

2.2.1.1. Cohort Study. This is the most definitive and expensive type of study and is based on identifying a group or groups of persons (cohorts) who are followed over time for the development of disease (or infection) in the presence or absence of suspected risk factors that are measured at the start of the study. These studies are usually carried out by identifying a cohort or usually two or more cohorts at the present time and then following them longitudinally over time. One cohort will be the group exposed to a risk factor or there may be several cohorts, each with a different degree of exposure. There usually is another cohort of unexposed persons who are followed in the same way. The cohorts are followed until the effect of the exposure occurs or the study is terminated for other reasons. If the occurrence of disease is the expected outcome, persons immune to the disease at the beginning of the study would not be included in a study cohort. This has been called a *prospective cohort study* or simply a *prospective study*. In infectious disease epidemiology, it may be possible to identify the persons in the cohort who are susceptible or immune at the start of the study by measuring the presence or absence of antibody in the initial serum specimens. Serial serum samples are then taken in which the appearance of antibody indicates the approximate time at which infection occurs. The occurrence of clinical disease at the same time provides information of the clinical–subclinical ratio. If the appropriate serum samples are taken and frozen, the actual testing can be delayed to the end of the study.

An alternative method of conducting a cohort study is to identify a group of persons at some time in the past who were presumably free of the disease under investigation at that time, as indicated by examining existing records. The cohort is then followed to the present, or even beyond, by measuring the occurrence of infection (by serological tests) or disease in that defined population. This approach is called a *historical cohort study* or a *retrospective cohort study*. Because the case–control study is also retrospective in terms of the time when the observations are made, it must be distinguished from the historical cohort study.

In a cohort study the statistical methods involve the calculation of the relative risk of the prevalence in the ill individuals as compared with the controls. This can be calculated using the format of a fourfold matrix as depicted in Table 1.

Table 1. Matrix for Calculating Relative Risk Ratios

	Number of persons		
Characteristic or factor	With disease	Without disease	Total
Present	a	b	$a + b$
Absent	c	d	$c + d$
Total	$A + c$	$b + d$	

If the frequency, $ala + b$, of the characteristic in persons with the disease (a) in this total group ($a + b$) is statistically significantly greater than the frequency of the characteristic in those without the disease ($c/c + d$), then an association may exist between the characteristic and the disease. For further details of the mathematical and epidemiological techniques and the biases involved in the selection of cases and controls, readers are referred to recent texts such as *Methods in Observational Epidemiology*.[18]

2.2.1.2. Case–Control Study. This has been called a retrospective study because it studies persons already ill with the disease and compares their characteristics with a control group without the disease for the presence or absence of certain possible risk factors. When a significant difference in the prevalence of a characteristic or risk factor is found, then the possibility of a causal association is suspected. Further studies using the cohort method are then often carried out to add strength to the association. The case–control study is usually the first type made because it is based on existing data, can be completed in a relatively short time, and is the least expensive. However, it cannot define the true incidence of the disease in relation to the various factors because the denominator at risk is not known.

A variation of the case–control study, and one encompassing the concept of a cohort study, is termed the *nested case–control study*. In this a large cohort is studied either prospectively or retrospectively for the occurrence of a specific disease, then these cases are matched by age and sex with persons in the original cohort who did not develop the disease. Various attributes of the two groups defined at the start of the study can then be compared. This method is very useful for diseases or conditions of low frequency in which analysis of the entire cohort would be an overwhelming task. An example of this is a recent study of Hodgkin's disease in relation to elevated levels of antibody to Epstein–Barr virus (EBV).[23] In this analysis, 240,000 persons whose sera had been collected and stored in four serum banks were followed for 5 years through cancer registries or hospital records for the development of Hodgkin's disease. Forty-three cases were identified in this manner and the EBV and other antibody levels were determined in sera from the group and compared with results from matched controls bled at the same time. A significant increase in certain EBV antibodies over those of controls was found 3–5 years preceding the diagnosis of Hodgkin's disease.

Biases may occur in case–control studies in the selection of cases, in the selection of controls, and in the elucidation of data by interview or records concerning the characteristics in question in both cases and controls. The selection of cases should ensure that they are representative of all patients with that disease. Ideally, this would assume that all patients with the disease seek medical attention, that the correct diagnosis is made and substantiated, that all medical facilities are canvassed, and that all cases are detected. In practice, these criteria are seldom met, and patients, for example, from a single hospital may be the only ones studied. This introduces a bias, since certain patients may be excluded from a given hospital because of such factors as age (e.g., no pediatric wards), socioeconomic level, or military or civilian status; the patient or physician may select a given hospital because of nearness, religious affiliation, the physician's privileges, nature of payment, or other considerations. These patients are not representative of all patients with the disease. The presence or absence of the characteristic under study may also influence the selection process for either the case or the control group or both, giving spurious associations.

Biases also are common in the selection of controls. Usually, controls should be selected from the same population group from which the patients are drawn and should be closely comparable to the cases in all known characteristics (age, sex, socioeconomic level, ethnic groups) except the one under study. Random selection from a large group may equalize those differences, but usually groups matched for certain variables or individuals matched carefully for paired comparisons are selected. However, if the two groups are matched too closely, the association between the cause and its effect may be masked. In a hospital setting, ill patients with diseases other than those under study are sometimes chosen. Bias may occur if some of these patients have diseases that are influenced by the characteristic in question. To limit this, patients with noninfectious diseases are often chosen in an infectious disease study. In a community setting, healthy controls may be advantageous. In matching, only those variables known to affect the disease should be selected. Each matching factor included, while controlling the results, eliminates the possibility of evaluating that factor itself.

To avoid bias regarding the presence or absence of a characteristic in the procurement of data by interview or from records, those charged with data collection should not know which is case or control, and the ascertainment should be uniform or standard. Once the data have been obtained, the odds ratio associated with a given characteristic is calculated from Table 1 by the cross-product of $a \times d$ divided by $b \times c$. This estimate is based on the assumption that the frequency of the disease in the population is relatively small and that cases and controls are representative of their respective ill and non-ill populations for that disease. Examples of case–control studies for an infectious disease would include the influence of some characteristic such as genetic makeup (HLA type), smoking, preexisting disease, or socioeconomic level as a

risk factor in a given disease. It should be emphasized that a particular risk factor might operate at different levels or at several levels: It might affect exposure and infection, the severity of illness after infection has occurred, the duration of disease, the development of complications, or the case-fatality rate.

The advantages of case–control studies as compared with cohort studies (see Table 2) include the relatively small numbers of subjects needed, their relatively high efficiency, the shorter time to complete the study, and their suitability for diseases of low incidence. Their disadvantages include difficulty in finding the needed information about the characteristic in question, or the inaccuracy of the information; bias in obtaining data; and bias in the selection of cases and controls. The appropriate selection of the control groups is probably the most difficult task.

2.2.1.3. Cross-Sectional or Prevalence Study. This third type of investigation examines the occurrence of disease and of suspected risk factors in population groups at a point in time or over a relatively short period of time. Prevalence rates among those with and without the exposure are determined and compared. This approach is usually limited to diseases of slow onset and long duration for which medical care is often not sought until the disease has progressed to a relatively advanced stage. Thus, the risk factors present at the start of the disease may be difficult to identify. This method is used for certain chronic diseases, such as osteoarthritis, chronic bronchitis, and some mental disorders,[24] but it may also be useful in certain infectious diseases such as those occurring in a hospital setting.

The reader should review more detailed descriptions of epidemiological methods such as found in Refs. 18–22 before undertaking any type of epidemiological study, as well as consult with a statistician in the planning stage to ensure the validity of the procedures and the adequacy of the number of subjects involved. See Section 5 for discussion of methods in epidemic investigation.

2.2.2. Experimental Epidemiology. In infectious diseases, this represents planned experiments designed to control the influence of extraneous factors, among those exposed or not exposed to an etiologic factor, preventive measure, or environmental manipulation by the investigator. One example is the planned introduction of an infectious agent in a controlled fashion into a group of animals or volunteers and the analysis of the spread of infection and disease within these groups as compared to a non-exposed group. Such studies offer the most scientifically controlled method of epidemiological study. Unfortunately, many bacterial species or agents may not induce infection or disease in animal models. Certain susceptible animals (marmosets, chimpanzees) may not be available for study or are too expensive. Volunteers are very difficult to utilize in today's

Table 2. Some Features of Cohort and Case–Control Studies

Features	Cohort	Case–control
Approach	Identify the subsequent incidence of disease in persons with or without given characteristic(s)	Identify the presence or absence of characteristic(s) in persons with or without a given disease
Starting point	Persons with or without certain characteristics	Ill persons and controls (healthy or with other disease)
Measurement	Incidence of infection or disease or both	Prevalence of characteristic
Type of observation	Serial, longitudinal surveillance of entire group for development of infection or disease or both	Single analysis by interview, records, or a laboratory test of the characteristic in persons with and without disease
Advantages and disadvantages		
Incidence	Can be measured directly	Not measurable directly
Risk	Direct assessment	Indirect assessment
Disease spectrum	Can be measured from infection to mild and severe disease in relation to characteristic(s) and to other diseases	Not measurable; a clinical case is the starting point
Factor(s) or characteristic(s)	Defined before disease develops	Factor(s) defined after disease develops
Bias	Little, usually, since information is recorded before the outcome is known, but problems in ascertainment, diagnosis, and follow-up may create bias	Bias may be present in interviewer, in patient, and in control; data from records may be incomplete
Attrition	Individuals may be lost to observation or refuse to be studied	Cases and controls may die prior to completion of study
Time	Often long period of observation	Can be short
Efficiency	Low except for diseases of high incidence	Comparatively high
Sample size	Large, depending on incidence of the infection or disease	Relatively small

ethical, legal, and social environment, and there are good reasons for these restrictions.

2.2.3. Serological Epidemiology. The systematic testing of blood samples from a defined sample of a target population for the presence of antibodies, antigens, genetic markers, specific cell-mediated immunity, and other biological characteristics is called a *serological* or *immunological survey*. It constitutes an important epidemiological tool. Serological techniques can (1) identify the past and current prevalence of an infectious agent in a community; (2) identify the incidence of infection by seroconversion or a rise in titer in samples obtained at two different times; (3) reveal the ratio of subclinical to clinical infections, when combined with clinical data; and (4) determine the need for immunization programs and evaluate their effectiveness as to the presence, level, and quality of antibody produced, its duration, and the degree of protection against disease. Serological techniques are useful in defining the incidence, clinical importance, and spectrum of illness of a new agent such as *Legionella pneumophila*. The presence of antibody or antitoxin to diphtheria, pertussis, and tetanus, as determined in a serological study, is a good reflection of the level of immunization and public health practice in a community. This is especially true of tetanus, since antitoxin is acquired almost solely through immunization and rarely, if at all, through natural infection. The use of serological surveys in areas where medical care, diagnostic facilities, and reporting practices are inadequate may provide information essential for the control and evaluation of immunization programs. The uses, advantages, and disadvantages of serological surveillance and seroepidemiology for viral infections are presented in Chapter 2 of the companion book[5] to this volume.

Seroepidemiology is more widely applicable to viral than to bacterial diseases because of the wider occurrence of demonstrable antibodies in viral than in bacterial infections and because of the better means to measure them. Nevertheless, these techniques have proved useful in variable degrees for brucellosis, cholera, diphtheria, legionellosis, leptospirosis, *Mycoplasma pneumoniae* infections, pertussis, Q fever, Rocky Mountain spotted fever, syphilis, tetanus, tularemia, and typhoid fever. Specific mention of their applicability will be found in the relevant chapters of this book. The development of monoclonal antibodies and diagnostic techniques, such as the enzyme-linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA), permits highly specific, sensitive, and rapid serological diagnoses. Development of sensitive and simple DNA probes and the ability to amplify DNA by the polymerase chain reaction (PCR) provide tools not only for diagnostic microbiology but also for the identification of antigens in stored paraffin or frozen sections.[6]

3. Epidemics and Their Investigation

Detailed descriptions of the concepts and methods of epidemic investigation can be found in a number of articles and book chapters.[24–26] An excellent recent article discussing the use of the case–control method in epidemic investigation gives a thorough review of the subject and an extensive table of examples.[27] This section will only deal with the highlights of epidemic investigation.

3.1. Pathogenesis of an Outbreak

Three essential requirements for an outbreak of an infectious disease are (1) the presence or introduction of an infectious agent by an infected human, animal, bird, or arthropod vector, or its occurrence in air, water, food, soil, or other environmental source, or its presence in or on a fomite; (2) an adequate number of susceptibles; and (3) an effective means of transmission between the two. Five circumstances in which epidemics occur can be mentioned: first, when a new group of susceptibles is introduced into a setting where a disease is endemic; second, when a new source of infection is introduced into an area from which the microbial agent has been absent and many susceptibles are therefore present, as in the return of visitors from a foreign country, or the arrival of new immigrants, or the contamination of food, water, or other sources of exposure by an agent not normally present; third, when effective contact is made between a preexisting infection of low endemicity with susceptible persons as a result of changes in social, behavioral, sexual, or cultural practices. Crowding as in a prison camp or institution or exposure of a new portal of entry are examples. A fourth possibility is an increased susceptibility to infection or disease or both through immunosuppression or other factors that influence the host response, such as a preceding viral infection, nutritional disorder, treatment with immunosuppressive drugs, or presence of a chronic disease. The devastating effect of HIV on the immune system has resulted in a worldwide epidemic of enormous and increasing proportions. A fifth circumstance might be the increase in the virulence or dosage of a microbial agent. This may have accounted for the massive outbreak of waterborne *Cryptosporidium* infection that occurred in Milwaukee, Wisconsin, in March–April 1993, which involved 404,000 infected persons of whom 4,400 required hospitalization.[28]

Epidemics or outbreaks are often classified from the standpoint of the source of infection. A common-source or common-vehicle outbreak may result from exposure of a group of persons to a single source of infection. This could be an exposure to a common source occurring at a single point in time, as in most foodborne outbreaks (point

epidemics), and characterized by a sharply defined and limited epidemic curve, often within the incubation period of the disease. It could be exposure on a continued or extended basis, as would be the case from a contaminated water supply or air source (airborne) and would result in an extended epidemic curve. In the latter setting, variations in the epidemic curve could result from differences in the dosage and time of occurrence of the microbial contaminant in the common vehicle or in the amount consumed, or they could result from changes in the frequency of exposure of the persons at risk to infection. The secondary spread of certain infectious agents from human to human in a common-source outbreak will also alter the epidemic curve, often producing a group of scattered cases after the initial epidemic wave subsides; these are called *secondary cases* and can lead to *tertiary cases*.

A second type of epidemic spread called *propagated* or *progressive* is due to multiplication and spread of an agent from one host to another. This is also called *contact spread* and may be direct, indirect, or by droplets (see Section 7). This is most often human-to-human spread, but could involve animal or arthropod intermediates. Here, the epidemic curve depends on the number of susceptibles, the degree of contact with an infected host, the incubation period of the disease, the mechanism of transmission, the portal of entry, and the infectiousness of the causative agent. In either common-source or propagated outbreaks, the epidemic decreases or stops when (1) the number of susceptibles effectively exposed to the source is diminished by natural attrition, by immunization, by antibiotic prophylactics, or by actual development of the disease itself; (2) the source of infection is eliminated; or (3) the means of transmission is interrupted.

3.2. Investigation of an Outbreak

The general strategy in the investigation of an outbreak includes establishing whether an epidemic actually exists, determining its extent, identifying the circumstances under which it occurred (e.g., time, place, person), evaluating its probable mode of spread, and initiating the steps to be taken for its control. Notification to appropriate health authorities should be made and help in epidemic investigation sought, if needed, from appropriate national or state disease control agencies; written reports should be prepared and distributed. News releases should be prepared to inform but not unnecessarily alarm the public. The epidemiologist, clinician, and laboratory experts all have roles in the analysis and management of an epidemic. The specific steps in epidemic investigations are presented in Table 3.

Table 3. Steps in the Investigation of an Epidemic

1. Determine that an epidemic or outbreak actually exists by comparing with previous data on the disease
2. Establish an etiologic diagnosis if possible; if not, define the condition epidemiologically and clinically. Collect materials for isolation and serological test, and data from sick and well-exposed persons
3. Investigate the extent of the outbreak by a quick survey of hospitals, physicians, and other sources and its basic epidemiological characteristics in terms of time, place, person, probable method of spread, and the spectrum of clinical illness. Prepare a spot map of cases and an epidemic curve. Call in outside help if needed
4. Formulate a working hypothesis of the source and manner of spread as a basis for further study
5. Test the hypothesis by determining infection and illness rates in persons exposed or not exposed to putative source(s) of infection by questionnaire, interview, and laboratory tests. Try to isolate the agent from the putative source(s)
6. Extend epidemiological and laboratory studies to other possible cases or to persons exposed but not ill
7. Analyze the data and consider possible interpretations
8. On the basis of the analysis, initiate both short- and long-term control measures
9. Report the outbreak to appropriate public health officials
10. Inform physicians, other health officials, and the public of the nature of the outbreak and the ways to control it

3.2.1. Determination of the Presence of an Epidemic. An epidemic or outbreak is usually defined as a substantial increase in the number of cases of a disease in a given period of time for that particular geographic area; e.g., an increase in the number of deaths from influenza and pneumonia that exceeds by 2 standard deviations the average experience for that week over the past 5 years is said to indicate an influenza outbreak.

A clinical diagnosis confirmed by laboratory findings is most important in determining whether a specific disease has exceeded the number of previously recorded cases. Unfortunately, a laboratory-proved diagnosis may be difficult or impossible to establish, especially early in an epidemic.

A clinical and epidemiological definition including the key features of the disease may be needed as a guide to reporting and for disease recognition until the etiologic agent is identified and appropriate methods are developed for isolation of the agent and/or its serological identification. Recent examples of the use of this type of definition are Legionnaires' disease, toxic shock syndrome, and AIDS. Even when the causative agent is known and laboratory tools for diagnosis are available, the disease may not be reportable, thus making comparison with past experiences impossible. On a practical level, any apparent concentration in time or geographic area of an acute illness of marked severity or with unique clinical features involving the respiratory,

gastrointestinal, skin, or central nervous system deserves evaluation. In the absence of a specific diagnosis, a simple working definition of a case should be established on the basis of available clinical and epidemiological data. It should be concise and clear-cut. The number of such cases should then be determined by a quick telephone or record survey of hospitals, clinics, and appropriate practicing physicians in the area. If the epidemic seems to be widespread, as with influenza, a random telephone survey of homes may give an estimate of the attack rate. The rate of absenteeism from key industries and schools may also help define the magnitude of the outbreak.

3.2.2. Determination of the Circumstances Under Which the Outbreak Occurred. This often involves two phases: a preliminary assessment based on available data and a more intensive investigation when the situation is better defined.

3.2.2.1. Preliminary Assessment. This is usually based on existing clinical records. In addition to the key clinical features, the age, sex, race, occupation, home and work addresses, unusual behavioral or cultural characteristics, date of onset, recent travel, and functions attended by others in the group in the recent past should be recorded. A time graph is drawn of the epidemic cases by date (and maybe time) of onset, from which the incubation period may be estimable. The time from the onset of the first cases to the peak may give a clue to this, as will unique or single exposures to the presumed source of infection. A spot map (place) may reveal clustering of cases or a relationship to a common source in the environment (food, water, air, anthropod). The data are analyzed to identify the persons at highest risk or some common denominator of risk and to postulate the most likely means of transmission. Early identification of a common-source outbreak is most important for instituting control measures. This might be a single (point) exposure, as in a food outbreak, or a continued exposure, as in a contaminated water supply. Person-to-person spread, airborne transmission, arthropod-borne spread, and zoonotic disease, especially of domestic animals, should be considered.

Appropriate materials for laboratory investigation should be collected early in the outbreak, such as throat washings, stool specimens or rectal swabs, blood for culture, and an acute-phase serum sample. A public health or hospital laboratory should be consulted in this endeavor. Since antibody to an infectious agent may already be present in many persons already ill in an outbreak, it may be desirable for baseline antibody levels to collect serum from other unexposed persons or from those incubating the disease, such as other family members or neighbors. A higher geometric mean antibody titer to a specific agent in ill compared to unexposed persons implicates that agent in the epidemic. Appropriate samples from the environment (water, food) or from possible vectors (mosquitoes, lice) should also be collected for isolating the agent.

On the basis of this preliminary assessment, a hypothesis of transmission may be formulated and recommendations for immediate control and isolation techniques made. Surveillance plans for identifying added cases may be drawn up, the appropriate environmental data assembled (water, milk, food, air), and questionnaires prepared for cases and controls (if a case–control study is to be conducted) in a fashion permitting easy analysis (marginal punch cards, computer). Standardized forms for foodborne outbreaks are available from state health departments and the CDC.

3.2.2.2. Intensive Study. This analysis should confirm or negate the hypothesis. The questionnaires prepared for this phase should include all possible circumstances under which the epidemic occurred and be administered to those ill, those exposed but not ill, and a comparable group neither exposed nor ill. Sera and other materials should be collected from these groups for antigen and antibody tests. The completed questionnaires may then be analyzed for comparison of attack rates (illness rate) in the three groups and as related to various risk factors. Antibody analysis of sera taken at the time of the outbreak and of those taken 2–3 weeks later may not only confirm the diagnosis but also identify the occurrence of infection in persons who were exposed but did not become ill. It may be possible to identify the specific nature of an ongoing outbreak by comparing the geometric mean antibody titer of those patients who are acutely ill with that of other patients already convalescing or by comparing the titer of those not exposed with that of those who are ill. More intensive study of the environment, insect vectors, and animal reservoirs may be needed. The analysis should include hypotheses to find the one that best fits the available data.

On the basis of this appraisal, control measures, including immunization programs, and other preventive measures should be initiated. Irrespective of whether the causative agent can be identified or not, the key element is the interruption of the chain of transmission. A written analysis of the epidemic should be given to the appropriate authorities. If no causative agent can be identified, then the acute and convalescent sera and material for antigen identification should be frozen for later study when new etiologic agents or laboratory techniques are discovered. A good example of the benefit of this procedure is its use in retroactively identifying several outbreaks of Legionnaires' disease that had occurred prior to the outbreak in 1976 in Philadelphia, from which the organism was first isolated.[29]

3.3. Example of Investigating a Foodborne Outbreak

An outbreak of illness characterized by diarrhea, abdominal cramps, and little or no fever involved 366 college students on February 24, 1966, in a new dormitory complex at the University of Wisconsin.[30] A quick assessment indicated that illness was confined to students who ate in three of six dining halls that served food from a common kitchen to 3,000 students. No other dormitories were involved, and the cases were sharply limited in time. The epidemic curve shown in Figure 1 indicates a peak incubation of 14 h. Stool specimens were obtained both from ill and healthy students and from food handlers. Samples of leftover items of food were not available; however, refrigerated samples of routinely collected food items were found for testing. Food menus for the preceding evening revealed that the three dining halls in which ill students had eaten offered a choice of fish or roast beef with gravy, whereas the other three dining halls had a choice of hamburger or fish; the other food items were common to all six dining halls. On the basis of this preliminary assessment, the hypothesis was formulated that this was a foodborne outbreak due to an agent with an average incubation period of about 14 h (range 10–20 h) that was present in or introduced into one or more of the food items served exclusively in the three dining halls where students became ill. The laboratory was notified of this as a guide to its tests. For more intensive investigation, questionnaires concerning foods eaten, time of onset, and the clinical symptoms were distributed to both sick and well students who ate in the three dining halls. They were returned by 366 ill and 740 well students, representing all the ill and two thirds of the well students. The clinical data indicated that the illness lasted less than 24 h and was characterized mainly by diarrhea; about half the ill students complained of abdominal cramps. Nausea, vomiting, and fever were rare. The average incubation period was too long for a staphylococcal toxin, and the clinical features would be unusual for *Salmonella* or *Shigella*.

An analysis of food items is given in Table 4. The evidence incriminating a food is usually based on the greatest difference in percentage ill between those who ate and those who did not eat a given food. In this outbreak, 69.9% of those who ate beef with gravy became ill compared to 4.9% who did not eat this item who became ill; furthermore, no one who ate beef without gravy became

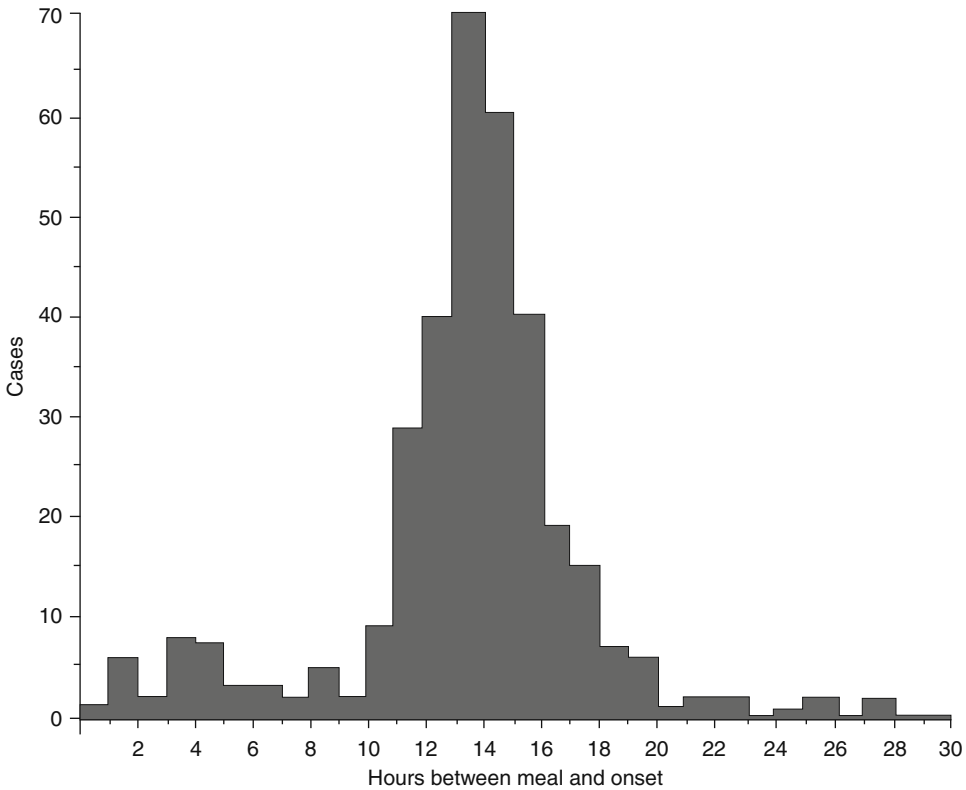

Figure 1. Epidemic curve of outbreak of *Clostridium perfringens* in a food outbreak involving 366 students at the University of Wisconsin. From Helstad et al.[30]

Table 4. Analysis of Attack Rate for Different Foods Eaten in a College Outbreak of Diarrhea[a]

	Ate food			Did not eat food			
		Ill			Ill		
Food item	Number	Number	Percent	Number	Number	Percent	Difference between ill and non-ill (percent)
Fish	391	16	4.1	715	340	47.6	–
Hamburger	188	15	8.0	918	351	38.2	–
Beef							
With gravy	479	335	69.9	627	31	4.9	65.0
Without gravy	48	0	0	1,058	366	34.6	–

[a]Derived from Helstad et al.[30]

ill, thus clearly incriminating the gravy as the likely source. The gravy as well as other foods available was negative on aerobic and anaerobic culture. Mouse-inoculation tests for toxin in the gravy were also negative; however, it was not known whether the gravy sample tested was from the incriminated meal or was set aside from a fresh gravy preparation. Laboratory analysis of fecal samples yielded the answer. Stool specimens from 19 of 20 ill students were positive for heat-resistant *Clostridium perfringens*, as was 1 of 24 stools from food handlers; no stools from 13 healthy students who had not eaten beef with gravy were positive. The organisms were isolated in thioglycollate broth after being heated 1 h in a boiling water bath. It was learned later that approximately 27 gal of bone beef stock had been kept overnight in the refrigerator in 9 gal plastic bags, mixed with 7 gal of fresh beef stock the next day, heated to a rolling boil, and served separately from the roast beef. Apparently, the inadequate heating of a heat-resistant preformed toxin in a very large volume of fluid had failed to destroy it. The control measures instituted were to prohibit future use of leftover gravy stock and to heat all items in smaller containers. *C. perfringens* food poisoning has an incubation period of 8–22 h with a peak of 10–14 h, closely fitting the outbreak described.

4. Agent

This book deals with microorganisms classified under "Lower protists (Prokaryotic): Bacteria." This grouping includes also the *Chlamydiae* (*Bedsoniae*) and the *Rickettsiae*, which are somewhat smaller than bacteria and are intracellular parasites.[31] Viruses, while classed as microorganisms, are sharply differentiated from all other cellular forms of life; they consist of a nucleic acid molecule, either DNA or RNA, that is enclosed in a protein coat or capsid. The principal groups of bacteria are presented in Table 5, which are derived from an "informal classification" presented by Jawetz et al.[31] in their excellent *Review of Medical Microbiology*, to which readers are to referred for discussions of microbiology, immunology, and host–parasite relationships. The new, beautifully illustrated book, *Medical Microbiology*, by Mims et al.[32] is also highly recommended.

The characteristics of microorganisms of epidemiological importance include those concerned with transmission through the environment, the development of infection, and the production of clinical disease. Table 6 summarizes some of these characteristics of bacteria, which include species pathogenic for humans.

4.1. Characteristics of Organisms That are Involved in Spread Through the Environment

For the spread of infection, a sufficient number of organisms must enter and survive transport through the environment to reach another susceptible host. Resistance to heat, UV light, drying, and chemical agents is important for survival of bacteria in nature. Some organisms such as *Vibrio cholerae* and *L. pneumophila* can survive for months in water, even in distilled water; others, such as *Bacillus anthracis*, attain survival through highly resistant spores. Organisms capable of actual multiplication within the environment in soil, plants, food products, milk, and elsewhere have an advantage for survival. The capacity to infect a nonhuman host such as animals or birds, or to be transferred through an insect vector such as the *Rickettsiae*, offers alternative pathways for the persistence and spread of microorganisms.

4.2. Characteristics of Organisms That are Involved in Production of Infection

Once bacteria have survived transport through the environment or intermediate host to reach a susceptible human host, several features of the bacteria are important in

Table 5. Key to Principle Groups of Bacteria Including Species Pathogenic for Humans[a]

Characteristics	Genera
I. Flexible, thin-walled cells with motility conferred by gliding mechanism (gliding bacteria)	
II. Same as I but with motility conferred by axial filament (spirochetes)	*Treponema, Borrelia, Leptospira*
III. Rigid, thick-walled cells, immotile or motility conferred by flagella	
Mycelial (actinomycetes)	*Mycobacterium, Actinomyces, Nocardia, Streptomyces*
Simple unicellular	
Obligate intracellular parasites	*Rickettsia, Coxiella, Chlamydia*
Free-living	
Gram-positive	
Cocci	*Streptococcus, Staphylococcus*
Nonsporulating rods	*Corynebacterium, Listeria, Erysipelothrix*
Sporulating rods	
Obligate aerobes	*Bacillus*
Obligate anaerobes	*Clostridium*
Gram-negative	
Cocci	*Neisseria*
Nonenteric rods	
Spiral forms	*Spirillum*
Straight rods	*Pasteurella, Brucella, Yersinia, Francisella, Haemophilus, Bordetella, Legionella*
Enteric rods	
Facultative anaerobes	*Escherichia* (and related coliforms), *Salmonella, Shigella, Klebsiella, Proteus, Vibrio*
Obligate aerobes	*Pseudomonas*
Obligate anaerobes	*Bacteroides*, Fusobacterium
IV. Lacking cell walls (mycoplasmas)	*Mycoplasma*

[a]Derived from Jawetz et al.[31]

the initiation and development of infection. One is the *infectiousness*, expressed as the ratio: number infected/number susceptible and exposed. A second is *pathogenicity*, a term used to denote the potential for an infectious organism to induce disease. It can be expressed quantitatively as follows: number with disease/number infected. The determinants of pathogenicity include mobile genetic elements such as plasmids, bacteriophages, and transposons.[33] The pathogenic process is complex and represents sequence of events in which many components are involved.[34] The adherence of organisms to host surfaces is a highly specific and essential step for subsequent events to develop. Epithelial surfaces provide appropriate sites for many bacteria. *M. pneumoniae* and *Haemophilus influenzae* find attachment sites in the respiratory epithelium, *Neisseria gonorrhea* in the urethral epithelium, and many enteric organisms (*V. cholerae, E. coli, Salmonella typhosa, Shigella flexneri*) in intestinal or colonic epithelium. Pathogenic organisms must possess characteristics that protect them against such host defenses as mucus and phagocytic cells. These protective features of the bacteria themselves include polysaccharide capsules (pneumococci, *Klebsiella, Haemophilus*), hyaluronic acid capsules and M proteins (β-hemolytic streptococci), and a surface polypeptide (*B. anthracis*). Toxins and certain extracellular enzymes may be important in the establishment of infection and in spread through tissues. The latter include collagenase (*C. perfringens*), coagulase (staphylococci), hyaluronidases (staphylococci, streptococci, clostridia, pneumococci), strepto-kinase or fibrinolysin (hemolytic streptococci), hemolysins and leukocydins (streptococci, staphylococci, clostridia, gram-negative rods), and proteases (*Neisseria*, streptococci) that can hydrolyze immunoglobulins, such as secretory IgA.[34] These surface properties and enzyme production contribute to the invasiveness of an organism.

4.3. Characteristics of Organisms That are Involved in Production of Disease

Disease is a rare consequence of infection. Usually, the presence of microorganisms on various surfaces of the body, their colonization on or in diverse epithelial cells, and their multiplication are unattended by signs of clinical disease.

Table 6. Bacterial Characteristics of Epidemiological Importance[a]

Epidemiological aspects	Bacterial characteristics
1. Features involved in *spread* through the environment	Number of organisms released by infected host
	Resistance to physical environment (e.g., heat, UV, moisture)
	Ability to multiply within environment
	Ability to infect intermediate host or insect vector
2. Features involved in initiation and development of *infection*	Host range of organisms
	Genetic makeup and antigenic diversity
	Infectivity of organism
	Pathogenicity of organism
	Number of organisms entering host and the portal of entry
	Enzymes involved in spread through tissues
3. Features involved in production of *clinical disease*	Most characteristics under (2)
	Virulence of organism
	Invasiveness of organism
	Production of endo- and exotoxins
	Immunopathologic potential

[a]Host attributes are considered in Table 7.

As with most viruses, infection without disease is a common outcome. However, since infection is a necessary basis for disease (excepting ingestion of preformed toxin), the attributes of organisms that are involved in infection are also important in clinical illness (see Section 4.2 and Table 6). The term *virulence* is used as a quantitative expression of the disease-producing potential of a pathogenic organism. Molecular studies of the determinants of virulence include how agents enter epithelial cells, a property that may be carried in different ways. In enteroenvasive *E. coli* it may be on a large plasmid, whereas for *Yersinia pseudotuberculosis* it is by a small DNA segment of the bacterial chromosome.[35] This property may be exchanged between bacteria, making noninvasive bacteria invasive.

Some organisms may lose apparent virulence if their structural identity is too close to the host's carbohydrates (for which the term *camouflage strategy* has been suggested). The factors that result in disease in an infected person are also determined by the host, as discussed in Section 6. Those that relate to the organism are invasiveness, the production of toxins, and the induction of an immune response that usually is beneficial but sometimes is detrimental to the host.

Invasiveness does not always correlate with disease and a widely disseminated organism does not always induce illness, but the wide distribution of a pathogen and its contact with many cells provide the potential amplification of any detrimental host response. That wide dissemination and a large number of organisms, even in the bloodstream, do not inevitably lead to toxemia is exemplified by the minimal host response evoked by large numbers of *Mycobacterium leprae* bacilli in the blood in lepromatous leprosy.

Organisms that produce endotoxins or exotoxins are likely to produce disease, since most are toxic to cells and evoke inflammatory responses. The exotoxins liberated by many gram-positive bacteria cause local cell and tissue injury; some damage phagocytic cells and thereby facilitate the spread of the organism. Examples include *Clostridium welchii, Clostridium botulinum, C. tetanus, Corynebacterium diphtheriae, S. dysenteriae, V. cholerae, B. anthracis, Bordetella pertussis, Streptococcus pyogenes*, and *Staphylococcus aureus*.[36] Some exotoxins are directly responsible for the characteristic clinical features of the disease, some are antiphagocytic, and some promote spread in tissues. They cause little or no fever in the host. Endotoxins are an integral part of the cell wall of gram-negative organisms. They are liberated in soluble form both during bacterial growth and presumably during death and disintegration of the organism. Endotoxins are strong immunologic adjuvants. They may produce fever in man and many other vertebrates; the pyrogenic action is mediated by a product synthesized by monocytes ("endogenous pyrogen") that acts on the thermoregulatory center in the hypothalamus. Other endogenous agents, such as prostaglandins and catecholamines, may also play a role. The lipopolysaccharide (LPS) is the most important component of endotoxin and is composed of a core polysaccharide common to many gram-negative bacteria, an O-specific polysaccharide conferring virulence and serological specificity, and a lipid A portion, mainly responsible for toxicity.[35] The effects of endotoxins appear to be mediated through leukotrienes, prostaglandins, and cachectin/TNF. Cachectin, which is identical to tumor necrosis factor,[37] is indistinguishable functionally from lymphotoxin, a product of activated T cells. This protein is produced by macrophages and by T cells in response to bacteria, viruses, and parasites and also occurs during cancers, resulting, in order of increasing dosage, in the following sequence of events: inflammation, cytotoxicity, cachexia, organ failure, irreversible shock, and death. There is a synergism between it and interleukin-1 in this phenomenon. Monoclonal antibody to cachectin/TNF can inhibit these responses and glucosteroids can also prevent endotoxin deaths. The gene for cachectin has been identified, and when put into hamster ovarian cells and then into nude mice results in cachexia. Despite these deleterious effects, cachectin/TNF in small doses appears to be beneficial in serving as a growth factor for macrophages

and as a tissue remodeler, a role for which it may have been designed in nature. It is not clear whether all these effects are mediated directly by cachectin/TNF or through mediators released by them. With large doses of endotoxins, there is also an effect that produces vascular collapse and death. Unlike exotoxins, endotoxins are heat-stable and are not fully convertible to protective toxoids. Endotoxins are normally released by many gram-negative bacteria in the intestines of healthy individuals, presumably absorbed in small amounts, and degraded by the Kuppfer cells. This occurs without pathological consequences on a continual basis and has a beneficial effect in stimulating the development of the immune system in the immature individual.[33]

Exotoxins are excreted by living cells, are quite unstable to heat, and consist of polypeptides of molecular weights from 10,000 to 900,000. They are highly antigenic and result in high titers of antitoxin that can neutralize the toxin. This antigenic property is useful in immunization with toxins rendered nontoxic by formalin, heat, and other methods. Different toxins produce disease via different mechanisms.[31] *C. diphtheriae* toxin results in inhibition of protein synthesis and necrosis of epithelium, heart muscle, kidney, and nerve tissues. The toxin of *C. tetani* reaches the central nervous system by retrograde axon transport where it increases reflex excitation in neurons of the spinal cord by blocking an inhibitor mediator. *C. botulinum* exerts its effect on the nervous system by blocking the release of acetylcholine at synapses and neuromuscular junction. Gut organisms, such as *Clostridium difficile*, produce a necrotizing toxin that leads to antibiotic-associated colitis, and that of *S. aureus* stimulates neural receptors from which impulses are transmitted to medullary centers controlling gut motility. *V. cholerae* toxin binds to ganglioside receptors on the villi of the small intestine, leading to a large increase in adenylate cyclase and AMP concentrations and the resulting massive hypersecretion of chloride and water and the impairment of absorption of sodium that characterizes the severe diarrhea and acidosis of cholera. Other toxins, such as that of hemolytic lysogenic streptococci, result in the punctate maculopapular rash of scarlet fever.

The production of clinical disease through immunopathologic mechanisms is more important for viral than for bacterial infections, but there are some examples of the latter. In streptococcal infections, antibodies may develop against an unknown component of the organism that is antigenically similar to heart muscle, leading to myocarditis. Immune complexes may also form, deposit in the kidney, and result in glomerulonephritis. In infections due to *M. pneumoniae*, the production of "heterophile" antibodies against human O erythrocytes (cold agglutinins) occasionally leads to acute hemolytic anemia. In primary infections by *M. tuberculosis*, the pathological picture is dominated by a vigorous and persistent cell-mediated immune response to the invading organism. The inflammatory, pathological, and immunologic processes of the host culminating in disease may be detrimental both to the host and to the microorganism. A successful parasite is one that leads to the least host response. For a more detailed discussion of microbial virulence factors, readers are referred to recent texts on infectious diseases and microbiology[32,38] and to recent articles.[34,39]

5. Environment

The external environment provides the setting in which the agent and host usually interact and is the usual means of transmission between the two. The effects of the environment on the organism itself are discussed in Section 4.1. The environment also contains the physical and biological mechanisms required for spread. The former includes air, water, and food and the latter animal, bird, and insect vectors. For some bacterial infections, the primary host is not man but some other living creature in the environment. This includes anthrax, brucellosis, leptospirosis, Lyme disease, Q fever, bubonic plague, Rocky Mountain spotted fever, salmonellosis, and tularemia. For infections involving insect transmission such as louse-borne typhus, Rocky Mountain spotted fever, and bubonic plague, the humidity, temperature, vegetation, and other factors in the environment may play a central role in limiting the occurrence of the infection to well-defined geographic areas favorable to the vector. Through climatic factors, the environment exerts an influence on exposure of the host to microorganisms. Warm weather and tropical climates result in recreational and occupational exposures to water, sewage, swimming pools, wild animals, and insects; they promote spread of skin infections in unclothed persons with abrasions on their skin. Certain organisms grow or survive better in warmer environments, especially enteric organisms. Intestinal infections flourish under such conditions. Inadequate refrigeration leads to foodborne outbreaks. Epidemics of Legionnaires' disease appear to depend on a chain of warm weather events. These include appropriate temperature and humidity for the organism to grow in soil or water, the contamination of a water-cooling tower or air conditioner, and airborne carriage or propulsion of the organism to susceptible humans, frequently in an enclosed environment (e.g., hotel, hospital, institution, club); July and August are good months for this.

The colder winter months, as well as school seasons in temperate climates of the northern hemisphere, bring individuals into close contact in a closed environment, facilitating spread of infections by the respiratory route. This includes bacterial infections of the central nervous system such as the meningococcus, *H. influenzae*, and pneumococcus organisms as well as true respiratory infections such as pertussis, bacterial and mycoplasmal pneumonias, tuberculosis, diphtheria, and streptococcal pharyngitis–tonsillitis. The peak period of different disease varies from one season to another. For example, pertussis and *M. pneumoniae* infections tend to occur most commonly in the fall and streptococcal infections in the spring. In addition, longer-term temporal trends in infection and disease occur within the same environment (as discussed in Chapter 2, Section 8.2). These changes reflect the complex interplay of agent, host, and environment. New strains of the organism, environmental alterations, varying behavioral patterns of the host, and the degree of immunization practice may change the pattern from one season to another.

The particular environmental setting—the macro- or microenvironment—also influences disease occurrence and its clinical patterns. In hospitals, certain types of skin, wound, and urinary infections are common, and their severity may be enhanced in persons who are already ill with another disease or are receiving immunosuppressive therapy. Antibiotic-resistant organisms are frequent in this setting. In prisons and in institutions for the mentally retarded or ill, low levels of personal hygiene and crowding contribute to the spread of respiratory, intestinal, and skin infections. Exposure in meatpacking and slaughterhouses or tanneries, or travel to developing countries, involves the risk of infection by various bacterial agents within that environment. With regard to children, the day-care center is posing an increasing hazard for them, as well as their parents for certain infectious diseases, especially respiratory and intestinal infections.[40] However, for young children infection is much more common than disease. For example, among 10,860 case contacts of an index case of *H. influenzae* type b infection in day-care centers, none of whom had received rifampin chemoprophylaxis, no clinical disease developed over an average 60-day observation period, although the carrier state was common.[41] Thus, rifampin prophylaxis of contacts may be unnecessary in these settings, although some other investigators disagree with this. For HIV infection, the environments of the brothel, the bar, and the bathhouse have provided ready transmission of this and other sexually transmitted infections, as has the "shooting gallery" of intravenous drug abusers. Travel to or residence in developing countries may result in exposure not only to specific tropical infections such as malaria, schistosomiasis, and cholera but also to many common respiratory and intestinal infections that the traveler might not encounter in a more hygienic setting. Even the homebody working in the garden or walking in the woods near home in endemic areas may be exposed to the bite of the deer tick or related species and become infected with *Borrelia burgdorferi*, the cause of Lyme disease.

6. Host

The occurrence of infection depends on exposure to a source of infection and on the susceptibility of the host. The development of disease in an infected person depends largely on factors intrinsic to the host, although some properties of the organism itself influence this. Some of the host factors are presented in Table 7.

They have been called the "clinical illness promotion factors."[3] Exposure to a pathogenic organism depends on characteristics of the human host that result in contact with sources of infection within the environment or that promote person-to-person spread. The behavioral pattern of the individual at different ages brings varying types of exposure in different seasons, cultures, and geographic areas. Personal habits such as intravenous drug usage or sexual promiscuity are also determinants of exposure. The family unit comprises an important setting for exposure and spread of infectious agents. The genetic background, nutritional habits, cultural and behavioral patterns, and level of hygiene within families create common patterns of exposure. The number and age of family members and the degree of crowding within the home also affect the transmissibility of infection. Hospitalization or institutionalization brings new exposures in closed environments. Heightened person-to-person contact and a mixture of susceptibles with infected or infectious individuals (carriers) underlie the increased risk of military recruits, children in day-care centers, and residents of institutions. Streptococcal, meningococcal, *M. pneumoniae, H. influenzae* type b, and enteric infections are common in such settings.

Occupational risks involve special types of exposures in certain occupations. The worker in the abattoir or slaughterhouse, meatpacking industry, or even at the butcher block is at risk to brucellosis, tularemia, and various parasitic infections. The sewage and sugarcane worker and the swine handler are exposed to leptospirosis, the tannery worker to anthrax, and the hunter to tularemia. The hospital worker is at increased risk to a variety of infectious agents, of which HIV is currently of greatest concern, although the risk is

Table 7. Host Factors that Influence Exposure, Infection, and Disease

Factors that influence exposure	
Behavioral factors related to age, drug usage, alcohol consumption	Military service
Familial exposure	Occupation
Hospitalization, especially intensive care	Recreation, sports, hobbies
Hygienic habits	Sexual activity: hetero- and homosexual, type and number of partners
Institutionalization: nurseries, day-care center, homes for the elderly and mentally retarded, prisons and other closed environments	Socioeconomic level
	Travel, especially to developing countries
Factors that influence infection, and occurrence and severity of disease	
Age at the time of infection	Entry portal of organism and presence of trauma at site of implantation
Alcoholism	
Anatomic defect	Genetic makeup, especially influences on the immune response
Antibiotic resistance	Immune state at time of infection
Antibiotic in tissues	Immunodeficiency: natural, drug-induced, or viral (HIV)
Coexisting diseases, especially chronic	Mechanism of disease production: inflammatory, immunopathologic, or toxic
Dosage: amount and virulence of organism to which person is exposed	
Double infection	Nutritional status
Duration of exposure to organism	Receptors for organism on cells needed for attachment or entry of organism

extremely small if universal hospital infection regulations are strictly followed. Hepatitis B infection is also of concern, and HBV vaccine should be given to all hospital staff exposed to blood or blood products.

Race does not usually influence infection if exposure is equal, but the response to infection may vary, such as the increased severity of tuberculosis in blacks. However, the separation of ethnic origin from other cultural, socioeconomic, behavioral, and genetic differences is often impossible. Recreational pursuits and hobbies influence exposures in both internal and external environments. The homemaker who prepares home preserves improperly may expose the ingestor to botulism; the home gardener or farmer is at risk to tetanus or Lyme disease, and the outdoorsman to various infections of wild animals. The influence of gender on occupational exposures has become of little importance, since women have entered almost all work areas including military life and many hazardous occupations. On the other hand, pregnancy is attended by special qualitative risks to infection, more commonly viral than bacterial, to which the male is not heir. Streptococcal B infections and syphilis are of special concern to the pregnant woman and her baby. Differences between the sexes in the portal of entry of microorganisms may result in different patterns of infection and disease, as is true in male homosexuals practicing passive rectal intercourse, in which the risk of infection with HIV is greatly increased. Genital lesions and discharges from sexually transmitted infections may also increase this risk in both sexes.

The socioeconomic level of the individual or the community affects the frequency, nature, and age at the time of infection. In developing countries and lower socioeconomic settings, infectious diseases, especially respiratory and enteric, constitute a leading cause of illness and death. The socioeconomic status influences infection and disease through a complex interaction of hygienic practices, environmental contamination, nutritional status, crowding, and exposure to animal and insect vectors.

Travel is an increasingly important risk factor because it may bring individuals into new settings, especially tropical or developing countries. Enteric infections are common hazards, especially toxogenic *E. coli, Campylobacter*, amebiasis, shigellosis, typhoid fever, salmonellosis, yersiniosis, and giardiasis. Enterotoxigenic *E. coli* (ETEC) is the most common cause and was found in 42% of diarrheal episodes in Latin America, 36% in Africa, and 25% in Asia. Other causes are various *Shigella* and *Salmonella* species. *Campylobacter jejuni, V. cholera, E. histoliticia, Giardia lamblia*, rotaviruses, and Norwalk-like viruses.[42] Mixed infections also occur. Bismuth subsalicylate had reduced the incidence of traveler's diarrhea by 65% in one study,[43] and its use is suggested for periods of up to 6 weeks.

Once infection has occurred, a number of factors influence whether clinical disease will develop and determine its severity (Table 7, part 2). Most of these factors are intrinsic to the host, although the dosage, virulence, and antibiotic resistance of the infecting organism play a role (see Section 4), as does the portal of entry. Entry sites that are close to vital organs or that permit easy access to invasion of the bloodstream may result in more severe and complicated infections. Among the host factors, age at the time of infection is an important determinant of the frequency of clinical illness

and its clinical features and severity. The presence of chronic diseases or other infections are risk factors. HIV infection greatly enhances the risk of opportunistic infections, of the reactivation of latent agents, and of malignancy.

Transmission of infection to the fetus in utero may result in fetal death or congenital abnormalities as with *Treponema pallidum*. Infections of the newborn such as those due to *Streptococcus B, C. botulinum*, and *Chlamydia trachomatis* may be severe and fatal. As is true in many viral infections, bacterial infections in childhood are often subclinical and less well localized than in the adult. The concept of "streptococcosis" illustrates this (see Chapter 34). In the newborn infant, respiratory involvement from group A infections is uncommon, although group B streptococci may cause sepsis and meningitis. In the age group 6 months to 3 years, group A infections have insidious development and mild symptoms. In the older infant and preschool child, a nonspecific streptococcal group A illness may be characterized by low-grade fever, irritability, and nasal discharge, sometimes accompanied by anorexia and vomiting. Clinical diagnosis is difficult. In the school-age child, upper respiratory infections due to group A predominate, and over half are manifested by the classic features of acute streptococcal pharyngotonsillitis: sore throat, often with tonsillar exudate, pharyngeal edema, dysphagia, enlargement of the anterior cervical nodes, and systemic symptoms (fever, chills, malaise). Another 20% may have milder and less localized illness, and 20% more may have either mild or no illness.

In general, the highest mortality from infection occurs very early in life, when immune defense mechanisms are immature, and in old age when they may be deteriorating. The clinical response to infection may also be more severe in conditions that alter or depress immune defenses. These include infection with HIV, organ transplantation, immunosuppressive drugs, and preexisting chronic disease, especially of the specific target organ of the infection; occurrence of a viral, parasitic, or other bacterial infection preceding or accompanying the current illness; and the prior use of alcohol or tobacco. The vigor and efficiency of the immune response may alter the host either favorably by control of the infection or unfavorably by certain immunopathologic processes. Genetic traits influence both susceptibility and disease. Their role in regulating the immune response is an important but often ill-defined one in relation to the occurrence and severity of the clinical disease. In tuberculosis, clinical illness among those infected has occurred more commonly in monozygotic twins and zygotic twins, even when other factors are controlled.[44] The nutritional level also affects host resistance. Malnutrition (especially severe protein deficiency) adversely affects phagocytosis and other primary defense mechanisms, the development of the thymus, and the efficacy of cell-mediated immunity against infections such as tuberculosis. In general, antibody formation is not impaired. The precise role of nutrition and vitamins in infection and disease is not well understood. Immunity is also influenced by vaccination, whether active or passive.

In summary, host factors may be divided into three major stages: (1) those that lead to exposure, (2) those that lead to infection among those effectively exposed, and (3) those that lead to clinical disease among those infected. The concepts of a clinical illness-promotion factor that leads to clinical illness[3] and of other, protective factors that result in subclinical or inapparent illness have been discussed.[4] Many of them remain unknown and they remain an important challenge to epidemiologists, microbiologists, immunologists, and geneticists.

7. Routes of Transmission

The major routes of transmission of bacterial infections are listed in Table 8 in general order of their importance. Many organisms have several routes. The sequence of spread usually involves the exit of the organism from the infected host; transport through the environment via air, water, food, insect, or animal, with or without bacterial multiplication; and the entry of a sufficient number of viable organisms into an appropriate portal of a susceptible host to initiate infection. For most infectious agents, specific receptors on the cell surface are needed to permit attachment and multiplication of the organism. Table 8 is loosely divided into human, animal–insect, and inanimate sources of infection in order to follow infection from its source to a human host, but the arrangement is sometimes artificial for those infections that exist primarily in other species or for those organisms that can multiply or survive in the natural environment.

7.1. Respiratory or Airborne

Organisms infecting the respiratory tract are either airborne via droplet nuclei or transmitted via droplets that are not considered true airborne transmission (see Section 7.2). The sources of the organisms carried by the air (droplet nuclei) include animate sources, the respiratory tract or oropharynx of infected persons, or from infected lesions of the skin, or from inanimate sources such as from water-cooling towers, as with *Legionella* organisms. Their success in reaching a susceptible host depends on the number of organisms present, the particle size, the force with which

Table 8. Transmission of Bacterial Infection[a]

Route of exit	Route of transmission	Examples	Factors	Route of entry
1. Human source				
1.1. Respiratory	Respiratory droplets or droplet nuclei	Bacterial pneumonias	Close contact or airborne	Respiratory
	RS and fomites	Diphtheria	Carriers	Respiratory, skin?
	Nasal discharges	Leprosy	Household contact	Skin, repiratory
	RS → droplets	Meningococcus	Crowding, military recruits, carriers	Respiratory
	RS → air, fomites	Pertussis	Direct contact	Respiratory
	RS → air	Plague (pneumonic)	Pneumonic case	Respiratory
	RS → droplets	Streptococcal	Close contact, carrier	Respiratory
	RS → droplet nuclei	Tuberculosis	Household contact	Respiratory
1.2. Skin squames	Respiratory, direct contact	Nosocomial bacterial infections	Hospitalization, surgery	Nose, respiratory, skin
	Direct contact	Impetigo due to staph and/or strep	Low socioeconomic level, tropics	Skin
	Close contact	Skin diphtheria	War wounds	Skin
		Yaws	Endemic foci	Skin
1.3. Gastrointestinal				
Enteric fevers	Stool → water	Cholera	Water, food, carrier	Mouth
	Stool → food	Salmonellosis	Food, animal contact	Mouth
	Stool → man	Shigellosis	Man to man only	Mouth
	Stool → water, food	Typhoid fever	Also food, flies	Mouth
Food poisoning	Food	Staph, *C. perfringens, Salmonella*, strep, *Vibrio parahemolyticus*	Inadequate refrigeration or cooking	
		Botulism	Home canning	Mouth
1.4. Urine	Water (swimming)	Leptospirosis	Infected animals	Skin
	Water	Typhoid fever	Poor sanitation	Oral
1.5. Genital	Sexual contact (hetero- or homosexual)	Chancroid	Mostly tropics	Urethra
		Chlamydia	Also carriers	Urethra, rectum
		Gonorrhea	Also carriers	Urethra, rectum
		Syphilis	Moist surfaces	Urethra, placenta
1.6. Placental	Congenital	Syphilis	Up to fourth month of pregnancy	Blood
1.7. Umbilical	Direct contact	Neonatal tetanus	Poor birth hygiene	Cord
2. Animal sources	Infected animal	Anthrax	Tanning	Skin, respiratory
		Tularemia	Skinning, dressing	Skin, eyes
	Bite of tick	Rocky Mountain spotted fever, Lyme disease	Outdoor exposure	Skin
	Rat flea	Bubonic plague	Infected rat	Skin
	Infected placenta via air	Q fever	Cows	Respiratory
3. Inanimate sources	Soil, air, water, food	Tetanus	Wound, childbirth	Skin
		Legionnaires' disease	Warmth, humidity, water coolers, air conditioners, potable water supplies	Respiratory

[a]This table is representative only and does not include all organisms. RS, respiratory secretions.

they are propelled into the environment, the resistance to drying, the temperature and humidity of the air, the presence of air currents, and the distance to the host. Some infections may be carried great distances from their sources, e.g., Q fever, tuberculosis, or Legionnaires' disease. As with viruses, respiratory-transmitted bacterial infections are difficult to control. The size of the particles in the aerosol influences its dispersion distance and the site in the respiratory passages at which the particles are trapped. Particles larger than approximately 5 μm in diameter are usually filtered out in the nose, while those up to 5 μm in diameter are deposited on sites along the upper and lower respiratory tract.

7.2. Contact

Contact transmission can be direct, indirect, or by droplets, which due to particle size are not truly airborne. Direct contact transmission means the agent is transmitted from an infected person or animal directly to a susceptible host; indirect contact transmission means the agent moves from the source to the susceptible host by means of an inanimate object. Droplets are infected particles more than 5 μm in diameter that only travel up to approximately 3 ft through the air before they infect a susceptible host or fall to a horizontal surface. Direct contact spread includes genital or sexually transmitted diseases, some gastrointestinal or fecal–oral spread diseases, and some other diseases such as tularemia resulting from contact with an infected animal.

Bacterial infections of the skin are transmitted usually person to person from an infected lesion or via squamae. They are commonly due to staphylococcus or streptococcus or a mixture of the two. They are manifested as boils, carbuncles, impetigo, and erysipelas. They are particularly common in warm and tropical climates and in settings of poor hygiene. Yaws, a nonvenereal, contagious disease of the skin and bones due to *Treponema pertenue*, is endemic in many tropical areas and is similarly transmitted; effective eradication programs with penicillin sponsored by the WHO have been carried out in many countries. Diphtheritic skin infections may also occur, especially in tropical climates, and may contaminate wounds.

7.3. Genital or Sexually Transmitted

The term *venereally transmitted* is now being limited to the five classic infections clearly transmitted by sexual intercourse (gonorrhea, syphilis, chancroid, lymphogranuloma venereum, and granuloma inguinale). The newer term, *sexually transmitted diseases* (STD), is broader, applies to both hetero- and homosexual activities, and encompasses all infections transmitted person to person during sexual activity. In recent years, *C. trachomatis* has been identified in this group as the cause of almost half of nongonorrheal urethritis (see Section 11.2.6 and Chapter 9), and *Ureaplasma* is under evaluation; enteric infections are of increasing importance in male homosexuals. The presence of ulcers due to STDs enhances the spread of HIV, especially a penile lesion from syphilis or herpes simplex.

7.4. Gastrointestinal or Fecal–Oral

The fecal–oral route of transmission is a close rival in frequency to respiratory spread and there are many sources of infection. A first group is called enteric fevers. Bacterial organisms from ill persons or carriers exit via the gastrointestinal tract to the external milieu for transmission via water, food, or direct contact to another individual. They constitute a major group of bacterial infections. The mouth is the common portal of entry. Some enteric infections involve only a human-to-human cycle, such as cholera, typhoid fever, and shigellosis. Others, such as salmonellosis, *Campylobacter* infections, and yersiniosis, also involve animal hosts. A variety of mechanisms may transmit the organism from the infectious stool to a susceptible person. Cholera is commonly transmitted by water, and on occasion by food (such as undercooked seafood like oysters and clams). Shigellosis is spread by the fecal route from patients or carriers and also by food, water, or flies. Typhoid fever is transmitted by food or water contaminated by the feces or urine from a patient or carrier and sometimes through contaminated shellfish or canned goods. *Salmonella* organisms are widely disseminated in nature and infect many domestic animals and birds, providing many potential sources of contamination of food and, less commonly, of water. *Campylobacter fetus* subsp. *jejuni* and *Yersinia enterocolitica* also infect many animals, including domestic ones such as puppies, and can infect exposed humans through direct contact or through water, milk, or food. For shigellosis, exposure to an infected human during the acute illness or shortly thereafter is the main source of infection; here, direct or indirect fecal–oral contact is usually more important than water or food. There is no extrahuman reservoir of infection.

A second group of gastrointestinal infections is called food poisoning. Here, contamination of food may occur from the feces of an infected person or carrier (food handler), but other sources of the organism are also common. The animal food source may be infected (i.e., *Salmonella* in chickens), or the organism may be present on the skin of the food handler (staphylococcus, streptococcus), in the environment (staphylococcus), in the soil (*C. perfringens, C. botulinum*), or in raw seafood (*Vibrio parahemolyticus*).

The transmission of enteric fevers and food poisoning is largely preventable. A good source of water, proper chlorination or boiling, frequent hand washing, appropriate refrigeration of foods, and thorough cooking are effective ways of interrupting the chain of infection. However, in developing countries and low socioeconomic settings, neither the means nor the education to carry them out may be available. Some may be prevented by immunization. Transmission of enteric infections by homosexual activity is a newly recognized and important problem in this group, and infection in HIV-infected patients may result not only from a wide variety of usual pathogens such as *E. coli* but also from organisms usually regarded as commensal and nonpathogenic such as the parasitic infection *Cryptosporidium*. However, this

organism caused a massive outbreak related to the public water supply of the city of Milwaukee in normal hosts.[28] This organism and other related ones are able to pass through usual water filters and are highly resistant to the usual levels of control. Increased surveillance of their occurrence in wells and public water systems is currently being carried out in several states under the auspices of the CDC.

7.5. Urinary

Urinary spread of infection is not common, but may occur in typhoid fever from an infected person and in leptospirosis from many animal hosts. Water is the common vehicle of transmission.

7.6. Perinatal

These infections occur at the time of childbirth. In *congenital infections*, the organism is transmitted *vertically* from an infected mother via the placenta to the fetus. Congenital syphilis, rubella, and toxoplasmosis are examples of this. Infections may occur *horizontally* from an infected cervix to the baby as it passes through the birth canal, as in gonococcal ophthalmia and chlamydial infections. Infections may also be acquired immediately after birth, as exemplified by tetanus neonatorum due to contamination of the newly cut umbilical cord by soil or a contaminated substance applied to the umbilical stump.

7.7. Insect Vectors

Rocky Mountain spotted fever is transmitted by the bite of the tick, which may remain infective for a long time, and the infection is maintained in nature by transovarian and transstadial passage. A mite has been implicated as the means of transmission of rickettsialpox from infected house mice. The transmission of bubonic (sylvatic) plague is through the rat flea (mostly *Xenopsylla cheopis*) from infected wild rodents. *B. burgdorferi*, the cause of Lyme disease, is transmitted by small Ixodes ticks, such as the deer tick, *Ixodes dammini*.

8. Pathogenesis

A section on pathogenesis is included in every chapter of this volume that deals with specific infections. Only a few concepts will be presented here. An excellent book by Mims,[35] entitled *The Pathogenesis of Infectious Diseases*, should be consulted for details, as well as more recent articles by him[36] and others.[33,34] Recent texts of medical microbiology[32] and infectious diseases[38] also contain excellent discussions.

8.1. Localized or Superficial Infections

Many bacterial infections produce diseases through the cells with which they first come in contact in skin or epithelial surfaces and remain limited to that area. Tissue damage results from the direct action of the bacteria, microbial toxins, indirect injury, inflammation, or immunopathologic processes. Most bacteria have specific attachment sites on epithelial surfaces (see Section 4.2). Examples of localized infections include diphtheria and streptococcal infections of the throat, gonococcal infections of the conjunctiva or urethra, cholera, and most *Salmonella* infections of the intestine. Many gram-negative bacteria have a limited capacity to invade tissues and tend to remain localized; some are able to invade only in debilitated, malnourished, or immunocompromised patients. Host antibacterial forces limit the spread of many bacteria. At the subepithelial level, three important defense mechanisms are called into play: (1) tissue fluids, (2) the lymphatic system leading to the lymph nodes, and (3) phagocytic cells (macrophages) in tissues and polymorphonuclear cells in the blood. Each of these mechanisms depends on the inflammatory response for its action,[35] as manifested by four cardinal signs: *warmth* and *redness* due to vasodilatation, *swelling* (vasodilatation and exudate), and *pain* (tissue distention, pain mediators). Polymorphonuclear cells enter, as well as macrophages and lymphocytes; exudation occurs. Tissue fluids provide plasma proteins, including immunoglobulins, such as IgG, complement, and properdin. The primary mediators of inflammation include histamine, 5-hydroxytryptamine, and kinins. Prostaglandins E and F are thought to play a role in the termination of the response. Microorganisms in peripheral lymphatics are rapidly carried to lymph nodes, where they are exposed to macrophages lining the sinus that act as a bacterial filter. Here, too, polymorphs, serum factors accumulating during inflammation, and the initiation of the immune response limit the infection. The phagocytic cells play a key role in the interaction with microorganisms, ingesting and killing bacterial invaders. Among the chemotractant factors for phagocytosis are platelet-activating factors, leukotriene B4, C5a, and certain formyl peptides.[33] The details are fully described by Mims,[32,36] as are the ways in which some bacteria are able to resist or interfere with phagocytic activity. Organisms that escape must still face one or two encounters with the macrophages, as well as other immune mechanisms, before successfully reaching the venous system.

8.2. Systemic Infections

Organisms that escape phagocytic cells and the other local defense mechanisms can spread through the tissues and, more distantly, via the lymphatics and the bloodstream. Some viruses (herpes, HIV, poxviruses, measles), some rickettsiae (*Rickettsia Rickettsii, R. prowazekii*), and some bacteria (*M. tuberculosis, M. leprae, Listeria monocytogenes, Brucella* spp., and *L. pneumophila*) actually multiply in macrophages. The toxins, enzymes, and surface components of bacteria that protect them against phagocytic destruction and promote invasiveness have been mentioned in Section 4. It is not clear what exact role the proteinases, collagenases, lipases, and nucleases produced by bacteria play in the pathogenesis of infection or which ones are related to nutritional and bacterial metabolism.

Lymphatic spread may occur from the lymph node, which serves not only as a focus of phagocytic and immune forces but also, if these fail, as a focus of dissemination. These results occur when the lymph flow rate is high from inflammation of tissues or from exercise of muscles, when the number of bacterial particles exceeds the filtration rate or the defense mechanisms of the node or both, and when phagocytic activity is impaired. In some instances, certain organisms such as *Pasteurella pestis* and brucellosis actually multiply in the lymph node and spread via efferent lymph channels. In other instances, vigorous inflammatory responses localize the infection, and the node becomes a graveyard of dead and damaged bacteria and of tissue cells.

Bloodstream or *hematogenous spread* is the most effective mechanism for the dissemination of an infection throughout the body. Bacteria may exist free in the plasma (pneumococci, *B. anthracis, Leptospira*), intracellularly in monocytes (*Listeria*, tubercle and leprosy bacilli, *Brucella*), or in association with polymorphonuclear cells (many pyogenic bacteria). The *bacteremia* may be transient and with little or no systemic response, as follows dental extraction in a healthy person; even a continuous bacteremia may exist with few toxic signs, as in leprosy where the organism exists in large numbers inside blood monocytes. On the other hand, severe systemic manifestations may accompany the presence of large numbers of organisms in the blood such as the pneumococcus, meningococcus, or group A *S. pyogenes*. This is called a *septicemia*. Bacteria may succeed in setting up foci of infection in areas where the blood flow is slow enough, or they may establish multiplication in sites previously damaged by disease or injury, such as *Streptococcus viridans* on abnormal heart valves producing subacute bacterial endocarditis, or staphylococci in the traumatized long bones of children may lead to osteomyelitis. Depending on the site of the infection, the liver and lung may receive many organisms during bacterial invasion of the bloodstream. The lung, liver, spleen, and bone marrow may also serve as important foci of dissemination of organisms, as in brucellosis, leptospirosis, and typhoid fever. Rashes accompany the dissemination of many viral and some bacterial infections to the skin. They may result from localization and growth of the organism in small blood vessels, producing thrombosis, infarction, and hemorrhage as in the rickettsial diseases, Rocky Mountain spotted fever, and typhus, as well as the petechial and purpuric lesions of meningococcemia. Immunopathologic processes involving sensitized lymphocytes, antibodies, and immune complexes play a role in many rashes, especially viral. A bacterial toxin may induce the rash as in scarlet fever. Some organisms such as *T. pallidum* in secondary syphilis extravasate from blood vessels and multiply in extravascular tissues. This results in highly infectious lesions that discharge to the exterior. Dissemination of *T. pallidum* to the blood–fetal junction in the placenta during pregnancy may result in infection of the fetus; slow blood flow in the placenta may contribute to this possibility.

Central nervous system (CNS) and meningeal involvement can occur by bloodstream carriage of the organism to the blood–cerebrospinal fluid junctions in the meninges or choroid plexus; from there, passive transport occurs into the flow of fluid from ventricles to subarachnoid spaces and throughout the CNS. Examples of bacteria that traverse this barrier and produce meningitis are the meningococcus, tubercle bacillus, *L. monocytogenes*, and *H. influenzae*. Actual spread along peripheral nerves has been shown for rabies and herpesviruses and is the means of centripetal passage of tetanus toxin.[45]

9. Incubation Period

The period of time from exposure to a source of infection to the first signs or symptoms of clinical illness is called the incubation period (IP). It varies with (1) the nature and dosage of the organism; (2) the portal of entry; (3) the type of the infection (localized or systemic); (4) the mechanism responsible for tissue injury (invasion, toxin, immunopathologic process); (5) the immune status of the host, being prolonged in the presence of partial immunity; and (6) other unknown factors individual to the host. The IP has many uses in epidemiology: (1) it helps define the etiologic agent in an epidemic; (2) it helps differentiate common source from propagated epidemics and identify the reservoir and/or source of the agent; (3) it delineates the period for which a person exposed to an infection is at risk to development of disease; (4) it assists in identifying the period of

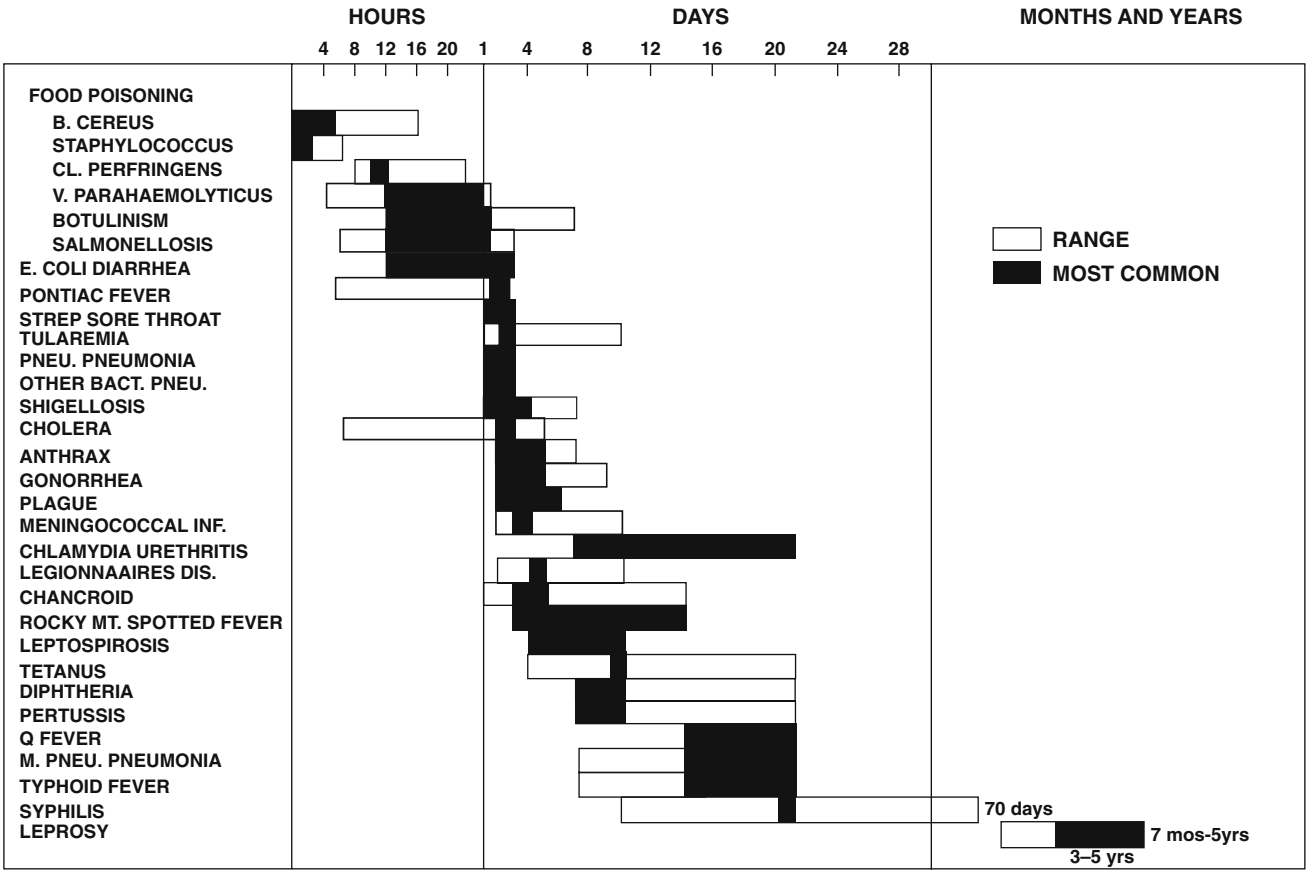

Figure 2. Incubation periods of common bacterial diseases. Derived from *Control of Communicable Diseases in Man*.[17]

infectiousness; (5) it provides a guide to the possible effectiveness of active or passive immunization; and (6) it gives clues to the pathogenesis of the disease.

The IPs of common bacterial diseases are given in Figure 2. Signs and symptoms due to preformed toxins or associated with food poisoning usually occur within 36 h after ingestion, sometimes as soon as 2–4 h, as in diarrhea due to *Bacillus cereus* or staphylococcal contamination of food. Traveler's diarrhea due to toxigenic *E. coli* has an IP of 12–72 h. Pontiac fever, the term used to describe an acute febrile disease without pneumonia recognized first in the Pontiac, Michigan, health department clinic and due to *L. pneumophila*, has a peak IP of 36 h, as compared to a peak IP of 5 days for Legionnaires' disease (pneumonia). It is not known whether this difference is due to a larger number of organisms inhaled in Pontiac fever (unlikely because of the comparative mildness of the disease), to dead organisms, or to some other factor.

Diseases due to direct involvement of epithelial surfaces have relatively short IPs, often under a week, such as streptococcal sore throat, bacterial pneumonias, shigellosis, cholera, gonorrhea, and chancroid. This is not invariably true, since diphtheria and pertussis both tend to have an IP of over a week, sometimes up to 3 weeks, and *M. pneumoniae* pneumonia has an IP of 2–3 weeks. These organisms may be less pathogenic. Diseases with longer incubation periods in the range of 2–3 weeks include systemic infections such as typhoid fever and brucellosis. The IP of syphilis most commonly is 3 weeks, although it may be as short as 10 days. Leprosy has an extremely long IP of 7 months to over 5 years.

10. Immune Response

A concomitant requirement for the evolution of multicellular life-forms was the development of methods for assuring the integrity of self. In the absence of the ability to recognize and cull out foreign cells, multicellularity could not have succeeded as a strategy. The mammalian immune

system is probably the most sophisticated antimicrobial defense in nature and represents the culmination of a billion-plus years of evolutionary refinement to the methodology of discriminating self from nonself.

Defense against microorganisms takes place at several levels in mammals. The term *innate immunity* refers to various features of an animal that confer natural resistance to invasion by microbes. These include physical barriers such as the skin and mucous membranes, chemical barriers (e.g., skin pH, lysozyme in saliva and tears), and the symbiotic bacterial flora of an animal that discourage colonization by pathogenic microbes.

Nonspecific immunity involves those processes in the immune response that do not react to specific individual foreign bodies and materials (antigens), but react to all foreign antigens with more or less equal vigor. The nonspecific immune system includes phagocytic cells, such as macrophages and polymorphonuclear neutrophils, the complement system, natural killer cells, cytokines such as the interferons and tumor necrosis factors, eosinophils, and basophils.

The third component of mammalian immunity is *antigen-specific immunity* or *adaptive immunity*. It is this component that appears to be unique among the vertebrates. Orchestrated by the lymphocytes, antigen-specific immunity recognizes foreign antigen in a highly specific fashion, expanding and activating only that subset of lymphocytes that can directly recognize and engage that precise antigen and no other. One of the most remarkable features of the antigen-specific immune system is the breadth of its capacity: The mature human immune system has been estimated to have the ability to respond discreetly to as many as a billion different antigens.

What follows is a very cursory overview of the components of the human immune system. For readers interested in more in-depth coverage, consult the general textbooks by Paul[46] or Kuby.[47]

10.1. Nonspecific Immunity

Nonspecific immunity plays numerous critical roles in the immune system. Many of the cells involved in nonspecific immunity participate in inflammatory responses and include macrophages, neutrophils, eosinophils, basophils, and mast cells. Overt tissue injury, whether caused by physical insult or invasion by a pathogen, stimulates the release of chemotactic factors that promote the migration and accumulation of various inflammatory cells at the damage site. Macrophages and neutrophils, particularly when activated by T-cell cytokines such as interferon-γ (IFN-γ), interleukin-4 (IL-4), and granulocyte-monocyte colony-stimulating factor (GM-CSF), are aggressively phagocytic cells. In the earliest phases of an infection, these cells serve to destroy bacteria and viruses and to mop up any debris, such as dead cells. Eosinophils are poorly phagocytic but are prominent in parasitic lesions, where they may be triggered to release a potent cocktail of enzymes and chemicals that destroy infecting parasites. Basophils and mast cells also have roles in immunity to parasites, but more as facilitators for the accumulation of other cells into a lesion.

Complement is a conglomeration of interacting proteins present in the bloodstreams of all vertebrates that have several important roles in nonspecific immunity. Various components of activated complement can promote and regulate inflammation, enhance phagocytosis through improved binding between the phagocyte and its target, and directly mediate cytotoxicity against cells and microbes. Several cleavage products of the complement activation cascade (C3a, C5a) have chemotactic and vasodilatory activity. A cleavage product of complement component C3, termed C3b, binds to specific receptors on macrophages and has lectin-like binding affinity for many bacteria, thus promoting opsonization. Complement activation culminates with the production of cannulus-like pores that self-insert into cell membranes (including those of bacteria), leading to colloid osmotic lysis.

Natural killer (NK) cells are a population of large granular lymphocytes that lack a receptor for specific antigen. They have a role in the immune surveillance of tumor cells and are capable of destroying their target cells by inducing apoptosis or programmed cell death.

Nonspecific immunity often serves to delay the progression of infection until the adaptive arms of the immune system have time to respond more specifically and effectively. Nonspecific immune mechanism is also frequently enhanced through the formation of partnerships with components of adaptive immunity. For example, specific antibodies may bind through specialized receptors to the surface of phagocytic cells, thus conferring antigen specificity to cells that otherwise have none. Cytokines secreted through the antigen-driven activation of T cells may enhance the level of activity of phagocytic cells or direct them to migrate to the site where they are needed. The activity of NK cells may also be enhanced by T-cell cytokines, particularly IL-2.

10.2. Humoral Immunity

There are two compartments of the immune system that are capable of responding specifically to foreign antigens. Humoral immunity, mediated by antibody molecules, is generated by B lymphocytes. Mature B lymphocytes bear specific receptors for antigen on their surface; the receptor on each circulating naive B lymphocyte is different from that

of all others, and each lymphocyte has one and only one specificity for an antigen. The receptor on the B lymphocyte is the immunoglobulin, or antibody, molecule itself, and upon activation, copies of this antibody are actively secreted. Since only those B lymphocytes that bind specifically with the antigens of a given bacterium or virus will be activated, the population of secreted antibodies that results is also specific for the invading pathogen.

With one limited exception, B-cell activation is absolutely dependent on the participation of T lymphocytes, which provide helper activity in the form of cytokines. T-cell cytokines are required for the activation of the B cell, for its differentiation into a plasma cell (the antibody-secreting cell), and for its proliferation (required to maximize the production of specific antibody). T-cell-derived cytokines also direct the class of antibody molecule that a B cell will ultimately produce.

Five distinct classes or *isotypes* of antibody molecules are found in the mammalian immune system, each of which has distinct roles in antimicrobial defense:

1. *IgM* has at least two important roles in humoral immunity. In monomeric form, it is expressed on the surface of all mature, naive B lymphocytes and serves as the receptor for antigen on those cells. In the circulation, IgM occurs as a pentamer, with five identical subunit antibodies bound together by a protein called J chain. IgM is the predominant antibody produced during the first exposure to an antigen. In serum, pentameric IgM has the highest binding avidity of any of the isotypes of immunoglobulin. It is extremely efficient at agglutinating bacteria and is an excellent opsonin, promoting phagocytosis by macrophages and neutrophils. In addition, IgM is the most effective antibody at activating complement.
2. *IgG* is the most abundant immunoglobulin in serum, making up 75% of the total serum antibody. It is the predominant antibody produced in a secondary or anamnestic immune response. Four distinct subclasses of IgG are recognized. All four subclasses of IgG can activate the complement cascade, although with widely different efficiencies. In addition, specific receptors for the constant region of all four IgG subclasses have been identified on a variety of cell types, including macrophages, mast cells, neutrophils, and lymphocytes. The combination of antibody with these other cell types either confers opsonic capacity or leads (in the presence of specific antigen) to the release of mediators. On lymphocytes, the binding of immunoglobulin molecules to such receptors appears to have regulatory functions, such as switching off the secretion of antibody. IgG is the only immunoglobulin that is capable of crossing the placenta, a process that is mediated by a specific receptor for IgG located on placental cells. In addition to its other activities, IgG is the most important neutralizing antibody in the serum, by virtue of its relative abundance.
3. *IgA* is the principal antibody found in local secretions. IgA antibody can be found in tears, saliva, milk, sweat, lungs, nasal passages, the urogenital tract, and the gut. IgA plays a crucial role in the defense of mucosal surfaces, neutralizing bacteria and viruses at local mucosa before they have an opportunity to invade. The presence of large quantities of IgA antibody in milk and colostrum enables the efficient transfer of maternal humoral immunity to newborn infants. IgA is incapable of fixing complement. It serves primarily as an agglutinating and neutralizing antibody.

   IgA in local secretions occurs as a dimer, bound by J chain. IgA transport to local mucosa is mediated by a molecule called the secretory piece, produced by cells adjacent to mucosal sites. IgA associates with the secretory piece on the cell surface and is endocytosed, transported across the cytoplasm, and deposited at local mucosa.
4. *IgE* makes up less than 0.01% of the total serum antibody. IgE is best recognized for its role in mediating immediate-type hypersensitivity, caused by the degranulation of mast cells and basophils in various mucosal tissues. IgE has an important role in the response against parasites. The purpose of the release of vasoactive substances when IgE bound to the surface of a mast cell or basophil encounters antigen is to enhance the accessibility of neutrophils and eosinophils, serum IgG, and complement to the site of parasitic infection.
5. *IgD* has no direct role in mediating defense against infectious diseases. It is present, together with monomeric IgM, on the surface of all naive B lymphocytes and appears to have a role in primary B lymphocyte activation.

10.3. Cell-Mediated Immunity

The second compartment of antigen-specific immunity is cell-mediated immunity (CMI). It is mediated by T lymphocytes. T cells are superficially indistinguishable from B cells. The T-cell receptor for antigen is structurally similar to the B-cell receptor, and yet the two cell types recognize specific antigen in fundamentally different ways. B cells recognize intact antigen and respond with the production of molecules that bear an exact copy of the surface receptor's binding site. T cells have no capacity for recognizing intact antigen. To engage a T-cell receptor, antigen first must be processed into small peptides, which are then inserted into the binding cleft of a major histo-compatibility (MHC) antigen. The MHC antigens are a highly polymorphic family of dual polypeptide proteins, at least some of which are expressed on nearly every cell type in the body. Because there are at least several hundred allelic variants of MHC antigens, and because no human being can express more than 12 different variants (up to two each of six different subclasses), the likelihood of two randomly selected individuals expressing the same panel of MHC antigens is remote in the extreme. Thus, the MHC antigens expressed by an individual to a very large extent define the property of self. This is particularly true for T cells. During the process of maturation in the thymus, nascent T cells undergo a rigorous selection process, and only cells displaying an antigen receptor that has a weak binding affinity for one or more self-MHC antigens are permitted to complete their differentiation into mature T cells. Cells with no affinity for self and cells with too strong an affinity, i.e., strong enough to activate a T cell on its own, are destroyed. When a foreign

peptide is inserted into the cleft of an MHC molecule, its affinity is altered. A small number of T cells, perhaps one in half a million, will bind to this altered MHC with a high enough affinity to activate. Thus, T cells are able to recognize and respond to minute changes in the normal display of self, as represented by an individual's unique collection of MHC molecules.

There are two general effector mechanisms for CMI. The first, cytotoxic T-cell-mediated lysis, is mediated primarily by the subset of T cells that express the protein CD8 on their surfaces. These T cells are restricted to their recognition of foreign peptide on the surface of a class I MHC molecule, which are present on most of the body's cells. Once activated, these cells recognize their specific combination of foreign peptide and MHC on a target cell and have two methods for dispatching the target. The first involves the deposition of perforin pores, which bear a striking resemblance to the terminal complement complex, onto the surface of the cell. The second approach is to induce apoptosis in the target, directing the cell to essentially commit suicide. Both processes result in the destruction of the target cell. Cytotoxic T lymphocytes (CTL), by virtue of their ability to discern the presence of foreign peptides from microbial pathogens inside of a cell, are ideally suited for the elimination of intracellular parasites such as viruses. They are also considered to have an important role in the elimination of tumor cells.

Another CMI mechanism is mediated primarily by the other main subpopulation of T cells, those that express the protein CD4 on their surface. These T cells are restricted in their recognition of foreign peptides on class II MHC molecules. Class II MHC antigens are normally expressed on only a few populations of cells in the body, chiefly B cells, macrophages, and dendritic cells. All of these cell types are capable antigen-presenting cells, since $CD4^+$ T cells also have the central role in the regulation of T-cell responses; the limited expression of class II antigens in the body is thought to reflect a safety restraint aimed at limiting the responsiveness of immune cells. In addition to providing helper activity to both B and T cells, $CD4^+$ T cells are typically recruited to the site of tissue damage and infection, where they coordinate and amplify the effectiveness of both specific and nonspecific arms of the immune system.

10.4. Cellular Interaction in Immune Responses

The immune system is arrayed with an arsenal of weapons capable of causing colossal destruction of tissues if left unchecked. While it provides an invaluable service in the defense against microbial invasion and the spontaneous development of neoplastic cells, extremely tight controls are required to ensure that its activities do not escalate to the point where they become deleterious to the host. As such, the level of intercellular interaction in the immune system is extraordinarily high. As mentioned previously, B-cell responses are generally not possible in the absence of T-cell help. If specific cytokines, such as IL-2 for proliferation, are not made available to the antigen-stimulated B cell, a suboptimal response will result. The generation of T-cell help, in turn, is absolutely dependent on the presence of a suitable antigen-presenting-cell-bearing peptide on a class II MHC antigen. Thus, the participation of at least three different cell types is required to mount an effective immunoglobulin response to antigen. Similarly, a CTL response requires the participation of both a helper T cell and an antigen-presenting T cell for the activation of both T-cell help and the naive CTL.

These cellular interactions take place in at least two ways. Transmembrane surface proteins on both participating cell types may come into direct physical contact, potentially sending an activation signal across the cytoplasmic membrane into both cells. An alternative unidirectional signaling method is to produce soluble hormone-like proteins known as cytokines that bind to a specific ligand on their target cell and send an activation signal across the membrane. A large number of cytokines have been identified and characterized, and each cytokine typically has more than one activity, often depending on the type of cell it engages.

Cellular interactions are not limited to the activation of immune responses. When a threat to bodily integrity has been eliminated, there is no continued need for a response. The action of down-regulating immune responses is termed *immune suppression*. T cells are also the critical regulators for immune suppression. Many of these functions of immune regulation appear to be performed by discreet subpopulations of specialized T cells. At last count, there are at least several functionally distinct subsets of helper T cells, a similar number of suppressor T cells, and so forth. In addition, functionality among T cells does not appear to be set in stone. There are circumstances in which $CD4^+$ T cells perform cytotoxic function and population of $CD8^+$ T cells that serve various regulatory functions. Thus, the complexity of interaction among cells in the human immune system is quite high, and a meaningful discussion of the current, admittedly limited, level of understanding of those interactions is beyond the scope of this overview. Suffice it to say that, under ordinary circumstances, these interactions serve as a system of controls that ensure the immune system will mount a transient, surgical strike against any disease threat.

Occasionally, elements of the interregulatory network break down, sometimes leading to autoimmune disease, a condition in which the immune system causes damage to

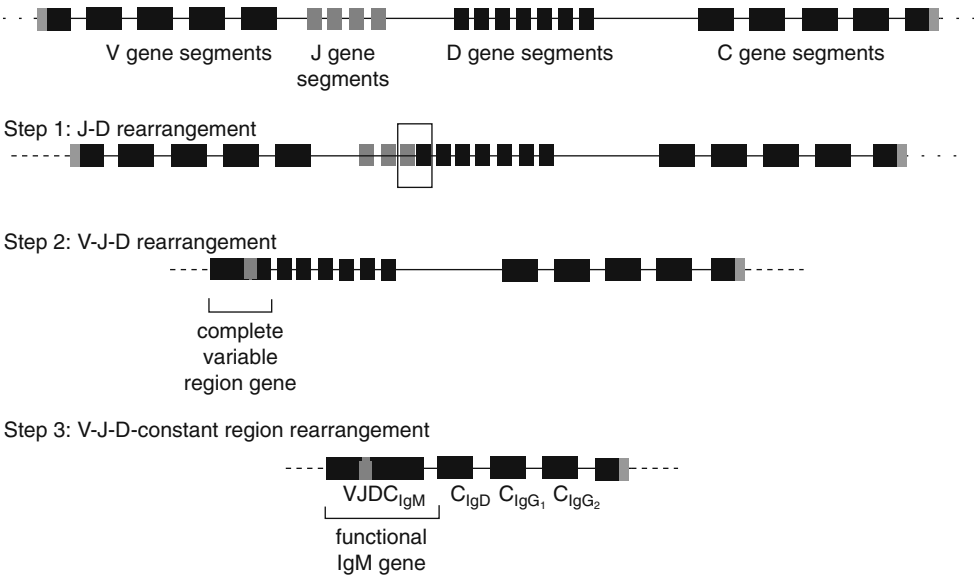

Figure 3. Immunoglobulin heavy chain gene cluster.

various host tissues. Such diseases include type I diabetes, rheumatoid arthritis, and systemic lupus erythematosus. Autoimmune diseases run the gamut from chronic disabling conditions to life-threatening diseases.

10.5. The Generation of Diversity in Antigen Recognition

The immune system presents a great enigma that was a matter of pure philosophical speculation until only two decades ago, namely how does the body go about the business of preparing a population of cells, each of which bears a distinct receptor for one of as many as a billion different antigens, none of which it has ever seen before? The two extremes of the philosophical argument went as follows: (1) One's genetic material contains the information required to encode all one billion different specificities for foreign antigen, and selects from that collection of genes in a random fashion; and (2) the genetic material encodes for only a few antigen receptor genes and the rest of the diversity results from extraordinarily high rates of mutation. The interesting feature of these two "obvious" solutions to the enigma is that neither of them came terribly close to the truth.

Immunoglobulin genes and T-cell receptor genes are arranged in clusters of subsegments, as shown in the illustration of an immunoglobulin heavy chain gene map (Figure 3). The immunoglobulin genes and T-cell receptor genes are assembled from randomly selected segments into a single functional gene. The construction of variable region (which encodes the antigen binding site) of a heavy chain gene, for example, would involve the co-alignment of one of approximately 1,000 V gene segments, with one of four J-segment genes and one of 12 D-segment genes. This results in $1{,}000 \times 4 \times 12 = 48{,}000$ possible heavy chain variable gene segments. The various segments are aligned through intrachain recombination events. Recombinational diversity for the immunoglobulin light chains is somewhat more limited, providing for approximately 1,000 different light chain variable genes. Since every functional antibody molecule is made up of two identical light chains and two identical heavy chains, the number of different combinations becomes $1{,}000 \times 48{,}000$ or 480,000. Added to that is the fact that the junction sites between V, J, and D segments vary, leading to junctional diversity due to single base substitutions and even short frame shifts. Finally, the mutation rate in the immunoglobulin gene cluster is approximately fivefold that of normal mutation rates. All of this is estimated to provide potential for diversity in the antibody population on the order of a billion different specificities. The T-cell receptors rearrange similarly.

11. Patterns of Host Response

The clinician usually deals with persons already ill with an infectious disease severe enough for them to seek medical care. The epidemiologist must study not only those clinically ill but also the full range of host responses that follow infection. These can vary quantitatively from inapparent infection

to severe illness to death in what is called a *biological gradient*. They can also vary qualitatively in different signs and symptoms that make up different clinical syndromes. The detection of persons with inapparent or subclinical infection requires laboratory tests to detect the presence of antibody or antigen.

11.1. Biological Gradient

When a susceptible host is exposed to a source of infection, a wide range of quantitative responses may occur.[4] These are often depicted as an iceberg, as shown in Figure 4, with the largest number of responses occurring subclinically, below the waterline of clinical recognition. The right side of Figure 4 represents the responses of the host. These range subclinically from exposure without successful attachment or multiplication of the bacterial organism, to colonization without tissue injury, to infection that evokes a host immune response but no clinical disease. The existence of these inapparent events can be recognized only by laboratory means such as isolation of the organism or measurement of the immune response. In viral infections, the ratio of inapparent–apparent (subclinical–clinical) infection has been determined through prospective studies correlating the number with an antibody response to the number clinically ill. The occurrence of inapparent infections is also suggested in persons with antibody but no history of clinical disease. Some information has also come from the rate of secondary infection in families with an index case and from volunteer studies. This type of information is not available for many bacterial infections because serological techniques are not as useful and/or widely employed in measuring infection rates, but a few examples may be cited. In leptospirosis, serological tests of persons heavily exposed (veterinarians, abattoir workers) but without known illness have shown an antibody prevalence of 16%. This suggests that only 16 of 100 exposed persons have been infected as manifested by an antibody response. There are no data for leptospirosis indicating the subclinical–clinical ratio, but of those clinically ill, 90% or so have an acute, self-limited illness without jaundice and with good prognosis; the overall case-fatality rate in 791 cases reported to the CDC from 1965 to 1974 was 7.7% (see Chapter 20). In tuberculosis, it was estimated that of the 50,000 clinical cases reported in 1963, 80% came from the 24 million infected in previous years and 20% from persons infected the same year (see Chapter 39).

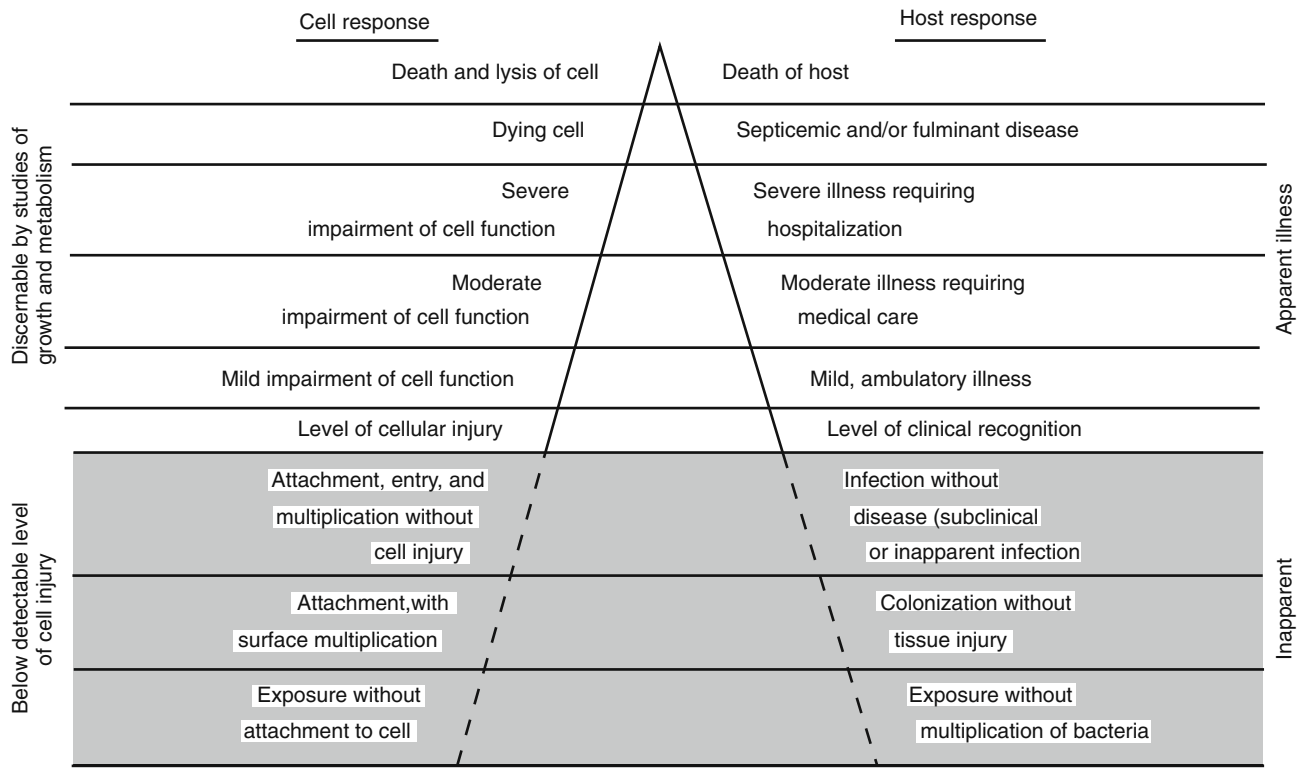

Figure 4. Biological spectrum of response to bacterial infection at the cellular level (*left*) and of the intact host (*right*).

In summary, a wide range of quantitative and qualitative responses can occur on exposure to a pathogenic organism. The determinants of this pattern lie both in the pathogenicity and virulence of the infecting organism (see Section 4) and in the age, genetic makeup, immune response, portal of entry, and other characteristics of the host (see Section 6).

The left side of Figure 4 is a simplistic expression of the response to bacterial infection at the cellular level. Cell injury may result from enzymes and other metabolic products of bacteria, from toxins produced by them, from entry and multiplication of the organisms intracellularly, as with *M. tuberculosis, M. leprae, B. abortus*, or as a consequence of the phagocytic and immunologic defense mechanisms induced by the infection. Epidemiologically, the message is that most organisms do not result in cell dysfunction or death and that the healthy person lives in symbiosis with millions of bacteria.

11.2. Clinical Syndromes

The host can show qualitative as well as quantitative differences in response to the same bacterial infection. These qualitative responses are manifested by different clinical syndromes, the patterns of which depend on the portal of entry of the organism, age of the host at the time of infection, immune status, and other factors. This variation is not as great with bacterial infections as with viral infections. Many bacterial infections such as anthrax, cholera, diphtheria, leprosy, pertussis, tetanus, tularemia, and typhoid fever present with fairly characteristic clinical features that vary quantitatively, but not qualitatively, from host to host, and a diagnosis can often be made on clinical grounds alone. Others, such as streptococcal infections, leptospirosis, syphilis, tuberculosis, and Lyme disease, may involve different tissues and organs in different persons, resulting in different clinical presentations, often depending on the site of infection and the age group involved. On the other hand, there are many clinical syndromes of diverse cause in which etiologic diagnosis is difficult on clinical grounds alone. It is here that epidemiological probabilities will help clinical judgment. Infections of mucosal and serosal surfaces fall into this category because of the limited spectrum of local responses that can result. These can involve the meninges, respiratory tract, intestinal tract, urinary system, and urethra. Invasion of the bloodstream (septicemia) by different bacteria also invokes a common group of signs and symptoms that may be difficult to differentiate etiologically.

This section will present some of the common causes of these clinical syndromes that may vary with the age of the person at the time of infection. Knowing the most common causes in a given age group may help to establish a tentative diagnosis and to initiate proper treatment.

11.2.1. Infections of the CNS. Meningitis is a common clinical syndrome caused by bacteria, viruses, fungi, and protozoa. The clues that suggest bacterial infections are polymorphonuclear leukocytosis in blood and cerebrospinal fluid (CSF) (500–20,000/mm^3), low CSF glucose concentrations (usually $<$35 mg/100 ml or CSF–serum ratio$\leq$0.5), elevated CSF protein (80–500 mg/100 ml), and in about 75%, the presence of bacteria in the Gram-stained smear of a centrifuged sample of CSF. These findings characterize purulent meningitis, but may be altered by treatment with antibiotics so that they resemble nonpurulent bacterial infections, such as *M. tuberculosis* and leptospirosis, or viral meningitis. The etiologic agents that produce meningitis in different age groups will vary some by geographic area, year, and socioeconomic level.

The age-specific incidence per 100,000 of various types of meningitis by age group is presented in Table 9 from an excellent review article on the diagnosis and management

Table 9. Annual Age-Specific Incidence of Meningitis, United States, 1978–1981[a]

Age	*Neisseria meningitidis*	*Haemophilus influenzae*	*Streptococcus pneumoniae*	Group B *streptococcus*	*Listeria monocytogenes*	Total meningitis
$<$1 mo	2.0	6.7	3.5	44.6	7.6	99.5
1–2 mo	9.1	18.6	5.7	10.0	1.3	56.7
3–5 mo	11.5	52.0	11.6	1.4	0.1	83.3
6–8 mo	10.6	65.1	8.0	0.3	0	88.4
9–11 mo	7.9	48.1	4.7	0	0.1	63.3
1–2 yr	3.8	19.0	1.5			25.3
3–5 yr	1.8	3.9	0.5			6.8
5–9 yr	0.7	0.7	0.3			2.0
10–19 yr	0.6	0.1	0.1			1.0

[a]Results are reported as numbers of children with meningitis per 100,000 population.[48] Data were provided by C. V. Broome, Centers for Disease Control, Atlanta, and by Schlech et al.[49]

of meningitis by Klein et al.,[48] which incorporates data from the CDC and a National Surveillance Study by Schlech et al.[49] The overall incidence of meningitis is highest in the newborn, drops in the first 2 months of life, and then rises to high levels between 3 and 8 months of life. Based on a National Surveillance Study of 18,642 cases reported from 1973 to 1981, *H. influenzae* accounted overall for 48.3% of the cases, *N. meningitis* for 19.3%, and *Streptococcus pneumoniae* for 13.3%, totaling 81%.[49] Rates in males exceeded females (3.3 vs. 2.6 per 100,000). By age, the most common causes were as follows: in the newborn, group B streptococcus and *E. coli*; in infants, *H. influenzae* type b and *N. meningitidis*; in toddlers, similar to the newborn; and in schoolchildren and adolescents, *S. pneumoniae, N. meningitidis*, and *H. influenzae* are the major pathogens in the decreased number of cases in that age group. An analysis of 493 episodes in 1993 of bacterial meningitis in hospitalized adults over 16 years of age in a Boston hospital from 1962 to 1988 revealed that 40% were of nosocomial origin with a mortality of 35%.[50] The risk factors included age $\geq$ 60 years, obtunded mental state on admission, and seizures within the first 24 h. Gram-negative bacilli (other than *H. influenzae*) caused 33% of these episodes. Of 296 community-acquired meningitis cases, *S. pneumoniae* accounted for 37%, *N. meningitides* for 13%, and *L. monocytogenes* for 10%. Only 4% of all episodes were due to *H. influenzae*.[50]

The characteristics of the organisms involved and the patterns of disease can be found in the individual chapters of this book. Suffice it to mention here that in the newborn, most cases of group B streptococci are due to subtype III, and that infection usually arises from vaginal and rectal infections of the mother that can lead to a 40–70% infection rate in the newborn; the K1 antigen of *E. coli* is involved in 75% of neonatal meningitis, and *L. monocytogenes* is becoming increasingly important in meningitis in this age group in several areas of the country.[48] In children beyond the newborn period, head trauma may precede the onset of meningitis and organisms may then enter through the cribiform plate or the paranasal sinuses. Meningitis may also follow neurosurgical procedures or osteomyelitis of the skull or vertebral column.

Acute bacterial meningitis is a medical emergency, and it is most important to establish the identity of the infecting organisms as quickly as possible as a guide to antibiotic therapy. However, until this is done, a Gram-stained smear of the CSF should provide a reasonable basis for initial chemotherapy.

11.2.2. Acute Respiratory Infections. These represent the commonest causes of morbidity in the developed world. Their importance as a cause of both morbidity and mortality in developing countries has now been recognized, and major programs of control have been initiated under the auspices of the WHO. In developing countries, it is estimated that over 4.5 million children under the age of 5 years die annually of acute respiratory tract infections (ARI), which represents some 30% of the 14 million deaths in this age group yearly.[51–54] The commonest causes are *S. pneumoniae* (see Chapter 34) and *H. influenzae* (see Chapter 16). A study of respiratory infections in children aged 0–59 months in several different developing countries revealed rates of 12.7–16.8 new episodes of ARI per 100 child-weeks at risk and 0.2–3.4 for lower respiratory tract infections.[55] Case management intervention strategies using community health workers have helped reduce the mortality, but many gaps remain in our understanding of the etiology, epidemiology, and pathogenesis of these conditions.

Fewer than 10% of acute upper respiratory infections (AURIs) are due to bacteria in either developed or developing countries, although in the latter, infections with *B. pertussis* (see Chapter 26) and *M. pneumoniae* (see Chapter 24) are important in certain settings. The syndrome of epiglottis in children aged 6 months to 2 years (up to age 6), however, is due to a bacterial pathogen, *H. influenzae* type b in about 90% of cases worldwide. This is often a serious and fulminant infection with a high mortality. A vaccine is now available.

The viruses involved in AURIs in both developing and developed countries are respiratory syncytial virus (RSV) in children under 3 years of age, parainfluenza in older children, and coronaviruses, rhinoviruses, and influenza in all ages.

The syndrome of acute pharyngitis and tonsillitis is due to streptococcal infections, mostly group A, in about one fourth to one third of cases, another one third are due to various viruses, and the remainder are of unidentified cause, although chlamydial infections may play a role in some of these.[56,57] Streptococcal infections can lead to acute rheumatic fever; this disease had been disappearing rapidly in developed countries until very recently when a recrudescence was reported in several areas of the United States. A very invasive streptococcal group A infection producing a toxic shock-like syndrome has recently been described in several parts of the world[58,59] (see Chapter 38). In developing countries, some 1.2 episodes of rheumatic fever are said to occur for every 1,000 untreated streptococcal infections, but this, too, seems to be decreasing.[52] *C. diphtheriae* (see Chapter 13) is also a cause of exudative tonsillitis in some Third World countries, and a recent outbreak occurred in Sweden involving 17 cases and 3 deaths despite very high immunization coverage.[60]

Acute lower respiratory infections are due mostly to viruses in young children, except for infants, to

M. pneumoniae and viruses in young adults, and to bacterial pathogens in older adults and the elderly. Prospective studies in community settings of developed countries suggest that five agents—RSV, parainfluenza virus, influenza virus, adenovirus, and *M. pneumoniae*—account for some 80% of acute lower respiratory infections in these population groups.[52]

Common respiratory syndromes in young children such as croup, laryngotracheitis, and bronchiolitis are usually due to viruses, especially RSV and parainfluenza viruses. Diphtheria may also cause a croup syndrome when the toxic membrane involves the larynx. Acute bronchitis is most often due to a variety of viral infections, but bacteria such as *M. pneumoniae, B. pertussis*, and *C. trachomatis* (TWAR strain) may also produce this syndrome. Chronic bronchitis, on the other hand, is largely associated with nontypable *H. influenzae* and pneumococci (*S. pneumoniae*).

Pneumonia is the sixth most common cause of death in the United States and has varied causes at varied ages. In infancy (under 6 months), about 30% are now recognized as chlamydial and present as a gradually developing nontoxic illness with cough, pulmonary congestion, rales, and patchy infiltrates on X-ray (see Chapter 10). Chlamydial genital infection of the mother carries a 10–20% risk of pneumonia in her infant. In another study of 205 infants under 3 months old hospitalized with pneumonitis, Brasfield et al.[61] identified a causal agent in 70%. *C. trachomatis* was found in 36%, RSV in 23%, cytomegalovirus in 20%, *Pneumocystis carinii* in 17%, and *Ureaplasma urealyticum* in 16%. In older children, the causes of pneumonitis and pneumonia are roughly one fourth viral, one third unknown cause, and the rest bacterial. More careful bacteriological culturing techniques have identified a bacterial etiology in 15–50% of this age group: pneumococci (*S. pneumoniae*) are the most common organism, and *H. influenzae* next most common; rarely, *S. aureus* and group A streptococci are involved.

A review of the bacteriological aspirates in children with pneumonia from many countries revealed a bacterial agent in 62% of 1,029 cases: *H. influenzae* and *S. pneumoniae* accounted for 54% of all isolates, while *S. aureus* was responsible for 17%.[52] Viral infections were associated with 17–40% of pneumonia in hospitalized children in several developing countries.[52] The true role of *Chlamydia* and *M. pneumoniae* infections in childhood respiratory infections in developing countries has not been well studied yet because of technical problems with the laboratory diagnosis, but it seems likely they may play as important a role as in developed countries. Community studies of *M. pneumoniae* pneumonia have shown the highest incidence in school-age children, with a decline after puberty, and with the lowest rates in the over 40-year-old age group, possible reflecting immunity. However, some 25–50% of pneumonia in young adults, such as college students, is due to this organism, and infection rates are high in military recruits (see Chapter 24). In a long-term study of some 15,000 episodes of pneumonia in a group health plan in Seattle, about 45% were tested for *M. pneumoniae* by isolation and serological tests, and 15% were found to be due to this agent, with the highest rate in children.[62] A new chlamydial strain, designated as TWAR (for Taiwan acute respiratory), has been shown to be an important pathogen in acute respiratory infections such as pneumonia, bronchitis, sinusitis, as well as mild upper respiratory infections.[63,64] In a retrospective examination of 200 patients from a group cooperative study,[62] 8% were due to this organism, which is a rate of 1 per 1,000 per year and with the highest incidence in the elderly. Only about 2% of patients with *M. pneumoniae* require hospitalization, and infection with *Chlamydia pneumoniae* is usually mild or asymptomatic. The secondary intrafamilial infection rate is high after an index case of *M. pneumoniae* is introduced and involves about 84% of children and 41% of adults.

In adults, especially older adults, most pneumonias are bacterial in origin. In the past, *S. pneumoniae* caused 50–90% of community-acquired pneumonias, but in recent years this has decreased to some 16–60%, still the dominant organism.[65–67] In an excellent prospective study of 359 community-acquired cases of pneumonia admitted to three Pittsburgh hospitals in 1986–1987, the most frequent etiologic agents were *S. pneumoniae* (15.3%), *H. influenzae* (10.9%), *Legionella* spp. (6.7%), *C. pneumoniae* (TWAR) (6.1%), and gram-negative organisms (6%).[65] In 32.9%, the etiology was indeterminate. No distinctive clinical picture was diagnostic for any etiologic agent. The underlying illnesses were immunosuppression (36.3%), chronic obstructive pulmonary disease (32.4%), and malignancy (28.4%). The median age was 62 years. The mortality was 13.7% and was highest for *S. aureus*. For most cases, erythromycin therapy would be effective. In recent years, gram-negative organisms are of increasing importance, perhaps causing 7–18% of pneumonia, and of special importance in the elderly. Some 30–40% of community-acquired pneumonias are of unknown etiology, due perhaps to 30% of persons unable to produce sputum for culture, or one third who have received antibiotics before hospitalization, or in about one fourth the organisms are difficult to isolate, such as *M. pneumoniae, C. pneumoniae, Coxiella burnetti*, and *Legionella* species, as well as viruses. Even invasive diagnostic techniques in three studies left 43% of unknown etiology, 8% were polymicrobial, and 49% were due to a wide variety of pathogens that varied according to geographic region.[67] Antibiotic-resistant organisms and toxic streptococcus are emerging pathogens in pneumonias, and *M. pneumoniae* is appearing as a pathogen in the elderly.[68]

11.2.3. Acute Otitis Media. This is a common infection of children, with a peak age of 6–18 months. It occurs seasonally throughout the year, but is highest in fall and winter.

Family aggregation is common for recurrent disease. Accurate diagnosis is dependent on cultures taken by aspiration from the middle ear. A recent review of etiology by Klein[69] reports that a bacterial antigen was isolated from two thirds of such aspirations: *S. pneumoniae* was the leading cause in 25–50%, then nontypable *H. influenzae* in 15–30%, *Moraxella catarrhalis* in 3–20%, group A streptococci and staphylococcus in 2–3%, and viruses alone or with bacteria in about 33%. *M. pneumoniae* was uncommon in middle-ear infections in most children. In children under 6 months, *C. trachomatis* with acute respiratory infections was found to be associated with middle-ear infections. It is important to emphasize that the etiology cannot be diagnosed by the clinical picture alone and that culture of aspirated material from the middle ear is needed.

11.2.4. Intestinal Infections and Intoxications. These may be divided into foodborne poisons and intestinal infections.

11.2.4.1. Bacterial Food Poisoning. While this section is concerned with bacterial causes, it is important to emphasize that Norwalk and Norwalk-like viruses are probably one of the major causes of both food- and waterborne outbreaks worldwide.[70] Bacterial food poisoning is dealt with in more detail in Chapter 5. In an analysis of 2,841 outbreaks of known etiology from 1973 to 1987 reported to the CDC and which involved 124,824 persons, 66% were caused by bacterial pathogens, 25% were due to chemicals, 5% to parasites, and 5% to viruses. The major contribution of bacterial etiology to the 124,824 cases was *Salmonella* (45% of total), involving 55,864 cases in 790 outbreaks; *S. aureus* (14% of total), involving 17,248 cases in 367 outbreaks; *Shigella* (12% of total), involving 14,399 cases in 104 outbreaks; and *C. perfringens* (10% of total), with 12,234 cases in 190 outbreaks. *C. botulinum* was reported in 231 outbreaks (8%) and affected 494 persons.[71] It should be emphasized that food outbreaks are greatly underreported.

11.2.4.2. Intestinal Infections. The causes of enteric infections vary with age and geographic area. They are perhaps the most common cause of morbidity worldwide, rivaling acute respiratory infections. In this book, they are dealt with under *Campylobacter* (Chapter 8), cholera (Chapter 11), *C. difficile* (Chapter 12), *E. coli* (Chapter 14), *Helicobacter pylori* (Chapter 17), salmonellosis (Chapter 31), shigellosis (Chapter 32), typhoid fever (Chapter 42), and yersiniosis (Chapter 43).

The magnitude, special settings, and etiology of diarrhea in both developing and developed countries have recently been reviewed.[72] The incidence in developed countries is estimated as 1–3 illnesses per person per year and 5–18 illnesses per child per year in tropical, developing countries. An estimated 12,600 deaths per day occur in children in some of these developing areas of Asia, Africa, and Latin America. In all countries the peak incidence is in young children, usually under age 3 years and often earlier in developing countries. The causes involve bacteria, viruses, and parasites, and sophisticated laboratory techniques are required to diagnose some of them, thus making definitions of etiologic patterns difficult in areas without modern laboratory facilities.

In children, viruses play a predominant role in some seasons, and the rotaviruses may cause about half the cases of acute diarrhea in children under age 3 years on a worldwide basis. In older children and adults, Norwalk-like agents are important, and intestinal adenoviruses are increasingly being recognized in young children. Among the bacterial pathogens, enterotoxic *E. coli* is probably the most common, with its production of both the cholera-like LT toxin and the ST toxin.[72]

In travelers, *E. coli* (ETEC) is also the most common cause and is found in 42% of diarrheal episodes in Latin America, 36% in Africa, and 16% in Asia.[42] The enterotoxigenic form has been found in 15–30% of illnesses in the community or in hospitals, especially in tropical, developing settings, and is also common in adults in these areas.[72] *C. jejuni* is perhaps the most common cause of inflammatory diarrhea in developed countries and *H. pylori* is increasingly recognized as a cause of gastritis, peptic ulcer disease, and probably gastric carcinoma.[73,74] The organism can be eliminated in 80–90% of infections by treatment with bismuth and antibiotics, and such therapy is routinely recommended for gastric ulcers.[75]

Diarrhea is increased in incidence in certain special settings. The importance of nosocomial diarrhea is being increasingly recognized. It accounted for 17% of all nosocomial infections in a children's hospital in Buffalo[76] and 42% in an adult intensive care unit in a London hospital.[77] The etiology of nosocomial diarrhea as reported to the CDC from 1980 to 1984 was *C. difficile* in 45.1% and *Salmonella* species in 11.8%.[72] In extended care facilities for the elderly, diarrhea is also an important problem, where about one third of patients experience a significant episode each year, and *C. difficile* is a common cause. Outbreaks of diarrhea in child care centers are also common, and frequent causes include rotavirus, *Shigella, C. jejuni, C. difficile, G. lamblia*, and *Cryptosporidium*. High attack rates are seen with rotavirus and some bacterial infections. Finally, some 50–60% of patients infected with HIV in the United States have diarrhea at the onset of illness, and initial

diarrhea is seen in over 90% of AIDS patients in Africa and Haiti.[78] A wide variety of organisms may be involved, of which *Cryptosporidium* is the most frequent, accounting for 3–21% in AIDS patients in the United States and 50% in Africa and Haiti.[78] This organism may also produce diarrhea in normal persons and its contamination of a public water supply in Milwaukee resulted in a massive outbreak involving over 403,000 persons.[28]

As mentioned above, *Campylobacter* enteritis is an increasingly recognized cause of intestinal infections in the United States, Great Britain, and Australia, accounting for some 5–14% of the cases in several large series (see Chapter 8). The clinical disease is characterized by watery diarrhea with mucus, blood, or pus, often cramping abdominal pain and fever, and sometimes gross blood in the stools of children. *Y. enterocolitica* is another recently recognized cause of acute diarrhea attended by some cramps, fever, and occasionally a rash; the incubation period is 1–3 days. There may be associated mesenteric adenitis, arthritis, and erythema (see Chapter 43).

The prevention of traveler's diarrhea is important because some 40% of travelers from developed countries with temperate climates will develop diarrhea, as reviewed by DuPont and associates.[43,79,80] The use of bismuth subsalicylate has proved useful in the short term and antibiotic prophylaxis and treatment is recommended for longer exposures. The following recommendations are quoted from DuPont et al.[79]:

> In most cases a bacterial pathogen is responsible for the illness. The antimicrobial agents with the greatest activity against these organisms are cotrimoxazole (trimethoprim/sulfamethoxazole) during the summer months in the interior of Mexico (a region where this agent has been studied extensively), and the fluoroquinolones for other places or other times, until data become available to indicate the appropriateness of cotrimoxazole here as well. Persons at risk should take along with them a drug to treat symptoms of travelers' diarrhea, and an appropriate antimicrobial agent. At the passage of the third unformed stool, it is recommended that travelers treat themselves with fluids and salt (flavored mineral water augmented with saltine crackers is sufficient in most cases), symptomatic treatment and antibacterial therapy. Of these, the antimicrobial is the most important component, which is given either as a single large dose or once or twice daily for 3 days. Perhaps optimal therapy for afebrile nondysenteric patients is loperamide in combination with the antibacterial drug. In the face of fever or dysentery, the antimicrobial should be used alone. In special situations where food and beverage restrictions cannot be followed and where the itinerary cannot tolerate even the slightest alterations because of illness, chemoprophylaxis can be considered. The most effective preventive medication in this case is the antimicrobial also used for therapy, taken in half the therapeutic dosage daily while in the area of risk. However, the majority of travelers should not use this approach.

11.2.5. Acute Urinary Tract Infections. In various studies of acute urinary tract infections (UTI) of inpatients and outpatients, *E. coli* is by far the most common organism in both settings, accounting for up to 80% of initial urinary infections in outpatients.[81] In a more recent compilation of etiologic agents in hospitalized cases, Andriole[82] found 35.8% due to *E. coli*, 16.4% due to *P. mirabili*, 16.3% due to *Enterobacter aerogenes*, 10.1% due to *K. pneumoniae*, and less than 6% each due to other causes. Over 80% are associated with use of urethral catheters. The spectrum of urinary infections varies and each syndrome has its own unique epidemiology, natural history, and clinical manifestations.[83] The major risk factors include the newborn (particularly the premature), prepubertal girls, young boys, sexually active young women, elderly males, and elderly females. Risk factors that contribute to lower tract infection in women include sexual intercourse, diaphragm–spermicide use, and voiding behavior.[84] UTI is the most common infectious disease of the elderly and is especially prevalent in debilitated, institutionalized older individuals. Unlike UTI in younger women, which tends to be related to frequency of sexual intercourse and is uncomplicated, in the elderly it is more difficult to treat and its pathogenesis is related to abnormal bladder function, bladder outlet obstruction, vaginal and urethral atrophy, use of long-term indwelling catheters, and puddling related to bed rest. The spectrum of organisms causing infection relates to the ecology of the patients' environments; those residing in nursing homes, and especially with permanent indwelling catheters, tend to have a greater variety of pathogenic organisms, many of which may be relatively antibiotic resistant.[85]

The immediate diagnosis of UTI is based on relatively simple techniques. The presence of pyuria and bacteriuria, the two most important indicators of UTIs, is most accurately determined by standard techniques. In quantitating pyuria, the finding of 10 leukocytes/mm^3 of urine by either hemocytometry or direct microscopy correlates highly with symptomatic, culture-proven UTIs.[86]

11.2.6. Sexually Transmitted Diseases. The term *sexually transmitted diseases* (STD) encompasses the five classic venereal diseases (gonorrhea, syphilis, chancroid, lymphogranuloma venereum, granuloma inguinale), plus other major ones such as HIV-1, HIV-2, human T-cell lymphotropic virus type I (HTLV-I), herpes simplex 1 and 2, papillomaviruses, hepatitis A and B, *C. trachomatis, Candida albicans*, and *Trichomonas vaginalis*. The number of cases and rates per 100,000 of major bacterial causes of STDs reported to state health departments in 1988 and 1992 are given in Table 10. While *C. trachomatis* infections are among the most prevalent of all sexually transmitted diseases, problems in diagnosis, lack of public health laws, and other problems have made surveillance of this disease

Table 10. Reported Cases and Rates per 100,000 of Classical Sexually Transmitted Diseases Reported to State Health Departments in the Civilian Population, United States—1988 and 1992[a]

	Number of cases		Rate per 100,000	
Disease	1988	1992	1988	1992
Gonorrhea	738,160	501,409	300.3	201.6
Syphilis (all stages)	104,546	112,541	45.5	45.3
Chancroid	4,891	1,886	2.0	0.8
Lymphogranuloma venereum	194	302	0.1	0.1
Granuloma inguinale	11	6	0.0	0.0

[a]Derived from Table 1, in Ref. 87.

incomplete, and therefore it is not included in Table 10. Reflecting increasing recognition and reporting of this infection, the rates per 100,000 have risen from 3.2 in 1984 to 182.6 in 1992 when 36 states reported to the CDC.[87] In large cities with more than 200,000 population the rates were 296.8 in 1992. An estimated 4 million cases occur annually, many of which cause pelvic inflammatory disease with serious sequelae such as ectopic pregnancy and infertility.

It is important to emphasize that many of these STDs occur in synergy with HIV infection and that the transmission of both is enhanced in the presence of the other. Overall, the trends in recent years show that reported rates for gonorrhea have declined 19%, with rates decreasing from 250 per 100,000 in 1991 to 202 per 100,000 in 1992, and with declines in primary and secondary syphilis rates from 17.3 to 13.7 in the same period. This decline may reflect the adoption of safer sexual practices. The proportion of adolescent women aged 15–19 years who reported having sexual intercourse, however, increased from 29% in 1970 to 52% in 1988.[88] The rates of gonorrhea and syphilis in the adolescent age group are three times that of the general population, and thus are a major target for education and control. The risk for STD is also much higher in blacks than in whites, with rates for primary and secondary syphilis being 60-fold higher and for gonorrhea 40-fold higher; for Hispanics the increases are fivefold and threefold higher, respectively.

Adequate surveillance data are not available for several sexually transmitted diseases. Some information of trends is seen in the office practice of certain physicians based on the National Disease and Therapeutic Index as analyzed in graphs in a CDC report.[87] For human papillomavirus genital warts, physician visits in this survey have risen from about 45,000 in 1966 to 200,000 in 1992. Trichomonal infections have declined slowly over this period, starting with 500,000 in 1966, but other vaginal infections have increased sharply from about 120,000 to 3,000,000.

Many of the newer agents of STD account for as many as or more infections seen in STD clinics or by private physicians than are accounted for by the classic causes. These infections are most common in the 15- to 30-year age group—the time of greatest sexual activity, especially extramarital. They are more commonly diagnosed in men, both because men tend to have more sexual partners than do women (except prostitutes) and because the lesions are more apparent in men. Multiple infections are common in both sexes, and gonorrhea and syphilis should be excluded by appropriate examination in every patient seen with an STD. The changing nature of and the increase in these infections have several causes, including the use of measures other than the condom for contraception, changing practices in heterosexual and homosexual activities, especially involving genital–oral and genital–anal contact, the importation of infection from Southeast Asia, and increased public confidence in the availability and effectiveness of antibiotic therapy.

The increasing importance of *Chlamydia* infections deserves further emphasis. Chlamydial genital infections include urethritis, acute epididymitis in men, and pelvic inflammatory disease in women; these are discussed in Chapter 10. Overall, about half the cases of urethritis in men are nongonococcal, and among male college students, this rises to 80–90%. *C. trachomatis* (immunotypes D–K) is responsible for 30–50% of symptomatic cases of nongonococcal urethritis (NGU) and is more common in white than in black men and in higher than in lower socioeconomic levels. Its incubation period is longer than that of gonorrhea, and symptoms of urethritis in males may appear 1–2 weeks or longer after penicillin or spectinomycin treatment for gonorrhea, involving one third to two thirds of these men. Oral therapy of NGU with tetracycline or erythromycin hastens recovery. There is no clinical counterpart of NGU in women who develop *Chlamydia* infections of the cervix with or without cervicitis, but this organism may be involved in up to 30% of pelvic inflammatory diseases in females.[89] The other agents of NGU in men are uncertain, although *U. urealyticum* is considered the cause of 10–20% of NGU cases. If laboratory facilities are not available for the diagnosis of *Chlamydia* infections in persons with NGU, both the case and the sexual partner should be treated with appropriate broad-spectrum antibiotic therapy (usually tetracycline or doxycycline) as though they had it. For detailed information on STD infections, see Chapter 9 on chancroid, Chapter 10 on *Chlamydia* infections, Chapter 15 on gonococcal infections, and Chapter 35 on syphilis. Viral causes are discussed in the companion book on viruses.[5]

11.2.7. Hospital (Nosocomial) Infections. These are infections acquired after an admission to a hospital

and are discussed in detail in Chapter 25. More than 2 million patients annually in the United States develop nosocomial infections. In the largest study to date, 5.7% of 159,526 patients in 338 hospitals developed a nosocomial infection.[90] Each such patient stayed an average of four extra days in the hospital, paying an extra $2,100 for each infection. Some 19,027 deaths were directly attributable to a nosocomial infection and it was a contributory factor in 58,092. In reports to the CDC's National Nosocomial Infections Surveillance program in 1991–1992, which involves 149 hospitals, urinary tract infections were the most common site (33.1%), followed by pneumonias (15.5%), surgical site infections (14.9%), and primary bloodstream infections (13.1%), and this order was similar irrespective of the size of the hospital. Among 71,411 isolates from all sites, *E. coli* and *S. aureus* were the most common (12% each), followed by coagulase-negative staphylococcus (11%), *Enterococcus* spp. (10%), *Pseudomonas aeruginosa* (9%), *Enterobacter* spp. (6%), and all other organisms 5% or less.[90] Unfortunately, the major nosocomial pathogens either are naturally resistant to clinically useful antibiotics or are potentially able to develop resistance. This includes both gram-positive organisms (*S. aureus, Enterococcus* spp.) and gram-negative organisms (*K. pneumoniae, P. aeruginosa*, and *Enterobacter* spp.).

12. Diagnosis of Bacterial Infections

Identification of the causal agent is essential to establish the etiology of a bacterial infection and as a guide to selecting appropriate antibiotic therapy. It depends primarily on (1) microscopic examination of exudates, body fluid, or tissues after staining (Gram's stain, acid-fast), or by dark-field examination or immunofluorescent-labeled antibody tests, or by the newer techniques for antigen identification such as counterimmunoelectrophoresis and latex agglutination, as used in respiratory infections; (2) appropriate bacteriological culture techniques; (3) a variety of new techniques to identify the antigen and a particular antigenic strain, many based on molecular methods; and (4) serological tests. Serological tests are not as commonly employed as in viral infections because of the ease and rapidity with which the diagnosis can often be established by smear and culture for most bacterial infections. For slow-growing or difficult-to-culture organisms such as *L. pneumophila*, the spirochetes, and the rickettsiae, serological tests play an important role in diagnosis. Animal inoculation may be required to identify fastidious organisms and the toxins of certain bacteria, and skin tests may be useful to diagnose infections that show delayed hypersensitivity.

This section will briefly review some of these techniques, but for more definitive information, see textbooks on laboratory methods,[91,92] medical microbiology,[32] or clinical infectious diseases.[38] An informative pamphlet on the services available from the CDC for the diagnosis of diseases of public health importance is available that indicates specimen collection, tests done, shipment instructions, and federal regulations on interstate shipment of etiologic agents.[93] All such specimens with proper justification and a completed request form must be submitted to the National Center for Infectious Diseases of the CDC in Atlanta by or through the state health laboratory with the knowledge and consent of the state laboratory director or designee.

An important decision for the physician is the differentiation of bacterial from viral infections on first examination in order to decide on the necessity of antibiotic therapy and as a guide to laboratory tests. This may not always be possible, but the presence of bacterial infections is suggested by the vigor and acuteness of the clinical onset, leukocytosis, and the presence of purulent lesions with polymorphonuclear cells. Nonpurulent responses to bacteria are seen in such diseases as brucellosis, tuberculosis, and typhoid fever. The presence of more than 10 white blood cells/mm^3 of urine by either hemocytometry or direct microscopy is indicative of an acute bacterial urinary infection,[86] as is the presence of white blood cells in the stool of a bacterial pathogen involved in diarrhea, or of polymorphonuclear leukocytes (not lymphocytes) in spinal fluid of a bacterial meningitis.

12.1. Collection of Specimens

The selection of the appropriate site from which to obtain the specimen, its collection prior to antibiotic therapy, and its transport to the laboratory in a manner to preserve the viability of any organisms present are three essential ingredients of successful diagnostic microbiology. The specimen should be taken from the site of the infection or from the body fluid most likely to contain organisms from the infected site. The collection should be made with sterile swabs and collecting units. Cotton applicator swabs are commonly used, but since cotton may be toxic to certain bacteria, a synthetic material such as calcium alginate is preferable. An adequate sample must be obtained to prepare smears and cultures and for special isolation purposes (viruses, fungi). Swabs may be inadequate for this purpose, and the fluid itself, or a washing of it (e.g., throat, nasal, lesion), may be needed for quantitative measurement, as in urine, to determine the number of organisms present. A syringe aspirate is desirable for anaerobic cultures of purulent lesions. Since most large laboratories have special sections for bacterial, viral, fungal, parasitic, and treponemal diagnostic

techniques, separate specimens for each microbiological group considered as a possible etiologic agent in a given infection should be collected. Special techniques may be needed to avoid contamination by normal flora in needle or surgical aspirations from a lesion or from a transtracheal or transurethral site.

To preserve viability, material from patients may be (1) inoculated into appropriate transport media directly at the bedside, for which purpose kits are now commercially available; (2) carried to the laboratory for immediate inoculation; or (3) preserved in a transport medium that maintains viability, prevents desiccation, and limits overgrowth of other organisms; media containing agar and charcoal are commonly employed (Stuart's transport medium or Arnie's modification thereof). If transport media are used, smears should be prepared separately at the time of collection with a separate swab because the agar in the transport medium makes this difficult. If viruses are suspected, a separate specimen should be collected and immediately frozen in dry ice for transport to the laboratory. Blood samples should be collected aseptically in amounts of 10–15 ml. If shipment to a laboratory is needed, the serum should be separated aseptically and forwarded preferably in the frozen state, but this will vary, depending on the infection. Infections of certain sites or with certain organisms may require special collection or transport methods or both; these are described in the appropriate individual chapters in this book or in books on bacteriological diagnosis.

12.2. Requests for Testing

There must be good communication between the physician or epidemiologist and the microbiologist. In the face of an outbreak, the epidemiologist is urged to consult with the laboratory prior to the investigation or have a laboratory specialist accompany the investigator to make the proper specimen collection and method of transporting it to the laboratory. The wide array of specialized laboratory techniques and culture media available makes it necessary that the laboratory be provided with information on a clinical and epidemiological assessment of the etiologic possibilities. The age, sex, clinical diagnosis (or at least the organ system involved), previous antibiotic therapy, and other pertinent patient information plus the site, time, and date of collection and method of transport to the laboratory of the specimen are helpful data to the laboratory worker in pursuit of the correct techniques to be employed. In return, the clinical microbiologist must provide periodic reports to help the physician in selecting appropriate therapy until the organism is fully identified and its antibiotic sensitivity determined.

12.3. Tests Employed

The details of laboratory methods are beyond the scope of this section, but a few comments will be made; specific techniques are mentioned in each chapter. The importance of a properly obtained and thoroughly examined Gram's stain of the exudate or body fluid cannot be overemphasized as a guide to initial therapy. For example, the etiology of some 85% of acute purulent meningitis cases and of many bacterial pneumonias can be identified by smear, especially if capsular swelling occurs in the presence of specific antisera. Simple microscopic examination of an unstained, uncentrifuged specimen of urine that shows bacteria indicates a quantitative bacterial count of 10^4–10^5/ml, and the morphology may point to the proper etiology. The examination of bacteria in fresh preparations or on culture, after staining with specific, immunofluorescent-labeled antisera, provides specific diagnosis of group A hemolytic streptococci, plague bacillus, and *E. coli*; it has also been useful in identifying the organism in acute meningitis, in cervical gonorrhea, and in primary syphilis.

The rapid detection of antigen in body fluids such as respiratory secretions and in urine is now being accomplished by immunofluorescence, counterimmunoelectrophoresis, enzyme immunoassays, DNA probe hybridization, and latex agglutination. Commercial kits are becoming rapidly available for many of these techniques.[94] A number of molecular techniques are now being used for both phenotypic and genotypic identification of organisms and are well reviewed in a recent article.[95] Those used for epidemiological studies of *phenotypic variants* include antibiotic resistance patterns (antibiograms), biotyping, bacteriocin production, serotyping, outer membrane protein analysis, phage typing, immunoblotting, and multilocus enzyme electrophoresis. The limitations of these techniques are that they do not take genetic exchange or mutations into account, are nonspecific, and are not widely applicable. Independent isolates of the same strain may vary in their phenotype. *Genotypic typing* methods are used to identify the genetic composition of the organism by study of chromosomal, plasmid, or transposon DNA. The techniques include plasmid profile analysis, restriction endonuclease analysis, ribotyping, pulsed field electrophoresis, polymerase chain reaction digests, arbitrarily primed polymerase chain reactions, and nucleotide sequence analysis. Variations in the reproducibility and discriminatory power of the two general methods differ; in general, those that involve genotypic methods are better. Their application permits identification of specific patterns of transmission of an organism, differentiation between reinfection and reactivation, and recognition of the geographic distribution of a particular

strain. The epidemiology of antibiotic resistance involves (1) R plasmid spread (inter- and intraspecies), (2) strain (clonal) dissemination, and (3) transposition of R genes into R plasmids or chromosomes. These many techniques now provide the epidemiologist the means for the rapid identification of many organisms, including the specific strain involved, so that transmission patterns can be followed. Of special interest are the so-called emerging infections, which in the United States include *E. coli* O157:H7 disease, cryptosporidiosis, coccidioidomycosis, multidrug-resistant pneumococcal disease, vancomycin-resistant enterococcal infections, and Hantavirus infections. Special surveillance and diagnostic centers have been established to monitor these infections.[96]

The culture media used will depend on the organisms suspected and whether they are aerobic or anaerobic. Blood agar plates and broth cultures are widely used as a starting point. See individual chapters for specialized media for specific organisms. A useful table indicating the bacteria found by common culture media (and the media used), by type of specimen (urine, respiratory secretions, genital, etc.), and the specialized media needed to detect organisms missed by these standard procedures is available in the appendix of a recent microbiology text.[32]

Once the organism is isolated its antibiotic sensitivity is usually determined and is useful not only in the selection of the proper antibiotic but also in "fingerprinting" the organism for epidemiological tracing. However, this is not necessary for some organisms that are known to be uniformly sensitive to certain antibiotics or that are uniformly resistant to all but one or two antibiotics. In vitro antibiotic testing is not always relevant to a particular infection, especially if the infection is due to mixed organisms. It often does not provide quantitative data or express the effect of an antibiotic on different points in the growth cycle of the organism, and the testing procedure may not include the antibiotic best suited to the clinical situation. The tests must be made on organisms obtained before antibiotic therapy is initiated. Despite these limitations, in vitro antibiotic testing is widely employed and is especially useful for organisms prone to develop antibiotic resistance such as staphylococci, enterobacteria, and *M. tuberculosis*.

The in vitro tests commonly employed are the disk-diffusion techniques in agar and dilution-sensitivity tests on agar plates or in tubes with nutrient broth. The disk procedure is simpler and more rapid, but the zone of inhibition cannot be directly correlated with the concentration of the antibiotic needed to inhibit growth of the organism in vivo. Antibiotic resistance to two antibiotics by disk diffusion does not exclude in vivo effectiveness of the combination; disk diffusion cannot be used for combinations of antibiotics.

The dilution tests provide quantitative data, permitting estimation of the minimum inhibitory concentration of the antibiotic as well as the minimum lethal concentration necessary for killing, which may differ from the minimum inhibitory concentration. The techniques used for dilution tests, however, may vary from laboratory to laboratory; the results are dependent on the size of the inoculum and the broth medium employed. Many laboratories now use automated broth microdilution susceptibility testing, which is rapid and has some economical and procedural advantages over both disk-diffusion and broth macrodilution methods.

As indicated earlier, serological tests have limited application for many bacterial infections. However, they are useful for a number of treponemal, leptospiral, and rickettsial infections. Some of the key tests are indicated in Table 11. Chlamydial infections, including the TWAR strain, are being increasingly recognized as a cause of a variety of clinical syndromes, especially of the respiratory and genital tracts, and microimmunofluorescence tests are available for both IgG and IgM antibodies as well as a genus-specific complement fixation test. Certain levels of titers of antibody are needed to be indicative of recent infection and differentiation between *C. trachomatis* and *C. psittaci* is not possible.

As with viral diagnostic tests, acute and convalescent serum samples should be collected for all bacterial serological tests and the sera tested simultaneously; a fourfold or greater rise in titer is indicative of recent infection. Remember that there is only one time to take the acute-phase sample—in early illness.

For legionellosis, the IgG immunofluorescence titer must reach 1:128 or higher to be significant because of nonspecificity at lower dilutions; similarly, only cold agglutinin titers of 1:64 or higher are regarded as diagnostic of *M. pneumoniae* infection, and even then only about 60% of hospitalized *M. pneumonia* patients are positive, depending on the severity of the infection. The presence of specific IgM antibody is often diagnostic of an acute infection, if demonstrable, as for *B. burgdorferi*, the cause of Lyme disease, but the laboratory diagnosis of this infection is subject to wide variation and standardization of procedures is badly needed. For rickettsial infections, both the organism itself and *Proteus* antigens are useful in serological diagnosis. In streptococcal infections, an increase occurs in a group of antienzyme tests but is too late to be useful diagnostically; a high titer is said to place the person at greater risk of developing rheumatic fever. In syphilis, a great variety of serological tests have been used, employing both nontreponemal and treponemal antigens. The VDRL test is most widely employed as an initial test and is highly sensitive and well standardized but lacks high specificity. The diagnosis can be confirmed by the fluorescent-treponemal-antibody absorption (FTA-Abs)

Table 11. Some Serological Tests Used in Bacteriological Diagnosis

Disease	Test antigen	Test(s)[a]	Comment
Brucellosis	Organism	Agglutination	Four strains
Legionellosis	Organism	IF	Twenty serotypes
Leptospirosis	Organism	Microagglutination, CF, hemolytic, IFA	Crossings occur; many types
Lyme disease	Organism	ELISA IgG, IgM	Needs standardization
Mycoplasma pneumonia	Organism	IF, TRI, CF	
	O rbc	Cold agglutinins	60% positive
Q fever	Organism	CF, agglutination	
Rickettsialpox	Organism	CF	
Rocky Mountain spotted fever	Soluble antigen	CF	
	Proteus strains	Weil Felix	Ox19+++, Ox2+++
		Agglutination	OxKO
Streptococcosis	Extracellular products	Antistreptolysin O, DNase	Confirm past infection
Syphilis	Nontreponemal	VDRL flocculation test	Presumptive
	Treponemal	Rapid reagent tests	Presumptive
		TPI, CF, FTA-ABS	Specific
Yaws	Same as syphilis	Same as syphilis	Cannot differentiate from syphilis
Tularemia	Organism	Agglutination	Often 1:640 or more
Typhoid fever	O antigen	Widal agglutination	≤Fourfold increase

[a]IF, immunofluorescence; CF, complement fixation; IFA, indirect fluorescent antibody; TRI, tetrazolium-reduction inhibition; VDRL, Veneral Disease Research Laboratory; TPI, treponemal immobilization; FTA-ABS, fluorescent-treponemal-antibody absorption.

or hemagglutination (MHA-TP) tests, which are highly specific and available at most state and a few large private laboratories, as well as at the CDC. The *Treponema pallida* immobilization test (TPI) test is a highly specific test but requires maintenance of a mobile, live treponemal antigen; it is available at the CDC. Yaws (*T. pertenue*) shares identical reactivities with *T. pallidum* and cannot be differentiated serologically. Typhoid fever results in increases to the H, O, and other antigens of the organism; an increase in O-antigen titer in the absence of recent immunization is indicative of recent infection. Skin tests may also be useful in diagnosis by demonstration of hypersensitivity to various bacterial antigens. They are commonly employed in tuberculosis, leprosy, nontuberculous mycobacteriosis, brucellosis, and tularemia.

12.4. Interpretation of Tests

The isolation of a bacterial organism from an ill person does not always represent a causal relationship. The organism could reflect (1) part of the normal flora; (2) a healthy carrier state; (3) contamination during the collection process; (4) a transient microorganism contaminating a body surface; (5) a dual or multiple infection, in which the organism isolated is not the one causing the clinical illness; (6) a laboratory error or mix-up; or (7) the true cause of the illness. The factors that point toward a causal relationship are (1) isolation in pure culture or of only one organism; (2) the presence of large numbers of the same organism; (3) the presence of the organism in direct smear from a lesion; (4) procurement from a site normally free of bacteria; (5) repeated isolation of the same organism; (6) demonstration of an immune response; and (7) history of possible recent exposure to the organism in an ill person, in travel, in occupation, or otherwise. The response of the patient to an antibiotic to which the organism is sensitive provides suggestive evidence that the organism caused the disease; but because other organisms are also sensitive to the same antibiotic, this cannot weigh too heavily. Clinical and laboratory judgment plus knowledge of the qualitative and quantitative behavior of human pathogens constitute the best grounds for deciding a causal relationship. It should be remembered that some organisms not usually regarded as pathogenic may cause disease in patients with naturally occurring or drug-induced defects in their immune defenses, or in patients infected with HIV.

On the other hand, the failure to isolate an organism does not exclude a bacterial etiology. Such "false-negatives" could result from (1) prior antibiotic therapy; (2) failure to obtain a specimen from the proper site; (3) collection at the wrong time; (4) a loss of viability during transport to the laboratory; (5) use of inappropriate media, temperature, gaseous

environment, or other conditions for growth of the organism; or (6) failure to hold the culture media for a sufficiently long time, as with certain *Brucella* species. For organisms difficult or impossible to culture, molecular tools such as the polymerase chain reaction are providing important techniques for direct diagnosis, but extremely careful laboratory procedures are needed to avoid cross-contamination and false-positive results.[6]

Serological tests are also subject to misinterpretation. False-positive rises can result from cross-reacting antigens, nonspecific inhibitors, double infection with the other organism causing the illness, and antibody response to vaccination rather than to natural infection. False-negatives, i.e., failure to demonstrate an increase in titer, can occur when the serum specimen is taken too late in illness, two samples are taken too close together to demonstrate a titer rise, the organism is a poor immunogen, the wrong antigen is used in the test, some inhibitor or nonspecificity (as in immunofluorescence tests) obscures a true rise, or the wrong type of test is used for the timing of the serum specimens. Serological tests are also not available for many bacterial infections. One of the common problems is the interpretation of a high IgG antibody titer in a single specimen. The demonstration of IgM-specific antibody is strong but not absolute evidence of a recent infection; it could result from reactivation. The presence of antibody to a rare infection, or to one not usually present in that area as in a returned traveler, or the history of some recent unusual exposure such as in hunting, a new occupation, or a visit from overseas friends also adds weight to the recency of that infection. Such problems are more common in viral and parasitic infections.

13. Proof of Causation

The classic postulates were suggested by Jakob Henle in 1840,[97] some 40 years before bacteria were discovered, and then further developed by his pupil, Robert Koch, in 1884 and 1890, after he had isolated *M. tuberculosis*,[98,99] as well as by Edwin Klebs.[100] A recent book has reviewed the development and subsequent changes in these postulates.[101] The postulates are presented in Table 12. While fulfillment of these postulates provides strong evidence of a causal association, the failure to fulfill them does not exclude this relationship. Even at the time of presentation in 1890, Koch himself recognized some of these limitations, especially the inability to reproduce some diseases in experimental animals. At that time, this was true of cholera, typhoid fever, diphtheria, leprosy, and relapsing fever, for which Koch felt it necessary to fulfill only the first two postulates. Since then, many other limitations have been recognized,[102] as our knowledge of microbiology, epidemiology, and pathogenesis has increased. These include recognition of the asymptomatic carrier state, which would invalidate the second postulate if an individual were carrier of organism A and his disease was caused by organism B. The concepts of multiple causation, of inapparent infection, and of the biological gradient of disease are also limitations. The postulates are not generally applicable to viral and parasitic diseases or for organisms that cannot be grown in culture or induce an immune response. Criteria are also needed for chronic diseases. In an effort to cover these various possibilities, a "unified" set of postulates based mainly on epidemiological criteria have been proposed.[103] It is clear that all postulates and guidelines of causation are limited by the technology available to prove them and by our knowledge of disease mechanisms at the time. The need for establishing guidelines for causation is ever present in the field of bacteriology, where the causal relationship between parasite and disease must be established for newly recognized diseases such as Lyme disease, Legionnaires' disease, Pittsburgh pneumonia, chlamydial pneumonia and urethritis, infant botulism, enterotoxic *E. coli* diarrhea, *H. pylori* and gastric ulcer and carcinoma, toxic shock syndrome, and streptococcal B infections in infancy. New causes for old diseases, new diseases from old causes, and new diseases with new causes keep appearing as our techniques for their isolation and identification improve.

Table 12. Henle–Koch Postulates[a]

1. Parasite occurs in every case of the disease in question and under circumstances that can account for the pathological changes and clinical cause of the disease
2. Occurs in no other disease as fortuitous and nonpathogenic parasite
3. After being fully isolated from the body and repeatedly grown in pure culture can induce the disease anew

[a]From Koch.[98,99]

14. Control and Prevention

The three major principles of control of infectious diseases are as follows: (1) eliminate or contain the sources of infection; (2) interrupt the chain of transmission; and (3) protect the host against infection or disease or both. Additionally, the environment may contribute to the occurrence of disease by its effect on any of the above three areas.

14.1. Environmental Control

The provision of clean and safe air, water, milk, and food; the proper management of sewage and garbage; and the

control of insect vectors of disease are regarded as not only essential to health but also a legal right in most countries. The extent to which they are attained depends on the economy, energy resources, political will, and educational level of the country.

14.1.1. Air. While many infectious agents are airborne on droplet nuclei or particles from infected hosts or environmental sources to susceptible subjects, effective control of this means of transmission has been most difficult to achieve. In open environments, it has been impossible to attain, and even in closed environments attempts to sterilize the air by UV light filtration, propylene glycol, and other chemical aerosols have met with very limited success. At best, control of the air currents generated by air conditioners, water coolers, and fans will help slow down spread of organisms such as *L. pneumophila, M. tuberculosis*, and staphylococci. For patient isolation, laminar-flow units have been effective if properly used. The pollution of air by automobiles and industrial sources does not carry a direct risk of infection, but may depress host defense mechanisms so that disease develops, as in persons with chronic pulmonary diseases.

14.1.2. Water. Improvement in our water supplies has been one of the major factors in the environmental control of infectious diseases, especially of enteric infections such as *Campylobacter*, yersiniosis, cholera, typhoid fever, amebiasis, bacillary dysentery, as well as waterborne viruses like Norwalk viruses. The details of water purification and treatment can be found elsewhere, but involve removal of extraneous materials by filtration, settling, and coagulation, the replenishment of oxygen by aeration, and disinfection by chlorination. Bacteriological and chemical standards for the purity of water have been established and are reinforced by governmental and legal regulations. The presence of *E. coli* in defined numbers per milliliter[2] is taken as an index of fecal contamination of water. However, its absence does not guarantee water safety, since organisms such as hepatitis A and E viruses may escape filtration and chlorination procedures, and more recently *Cryptosporidium* cysts escaped a filtration system in a public water supply in Milwaukee, causing a massive outbreak of diarrhea involving over 403,000 persons.[28] This organism is also resistant to tolerable levels of chlorine. For the traveler, treatment of water with chlorine-release tablets or a drop of Lugal's iodine solution per quart of water 30 min prior to use or by boiling for 5 min (portable heating units can be purchased) will decrease the likelihood of acquiring bacterial intestinal infections in developing countries. Small millipore filter kits are also available for the traveler and are said to remove bacteria, *G. lamblia*, and even some viruses. Should these methods not be available, one can allow the water to run until very hot, collect it, and then use it for drinking water. Bottled water, wine, and beer or other bottled or canned beverages are usually safe.

14.1.3. Sewage and Garbage. Sewage water carries fecal material, industrial and chemical products, and other waste products. It must be safely conveyed without human hazard to septic tanks or to reprocessing, filtration, and activated sludge treatment centers, but has not posed a problem of infectious disease unless cross-contamination with water pipes occurs. The dumping of untreated sewage into streams, rivers, and the open sea is detrimental to fish and marine life and esthetically distasteful and impairs recreational use of such waters. It might result in transmission of certain intestinal pathogens via raw seafood to humans, such as the hepatitis A or E viruses, cholera, or *Cryptosporidium* in water itself. Clams and oysters have been responsible for many outbreaks of this sort, and thorough cooking is needed to kill organisms such as cholera or hepatitis viruses.

The proper disposal of the large amount of garbage, refuse, and other solid waste products produced by our modern society is an increasing challenge to proper land use and modern technology. Direct discharge into the sewage system after grinding and flushing is one method; compactors of garbage and waste material are now available even for home use. If stored and carried elsewhere for disposal, this must be done in closed, stable containers that protect against rats, flies, and other predators. The separation and recycling of certain reusable products such as glass, bottles, paper, and cans is to be encouraged. Large incinerators for burning garbage and refuse provide a safe but energy-expensive procedure. Landfill sites in communities are increasingly scarce, costly as land values increase, and objected to on esthetic grounds. Disposal of radioactive and other toxic wastes generated by medical, industrial, and energy uses in oceans raises international concern about the long-term food and energy potential of oceans, and land or tank disposal, especially of nuclear wastes, is unacceptable to most communities. The increasing uses of pesticides, and domestic and wild animal wastes in streams or rivers that may wash down into public water supplies, pose an increasing threat.

14.1.4. Milk and Food. Milk and food must be protected against contamination at their source, during transport and storage, and in their preparation for consumption. Cows must be free from tuberculosis, brucellosis, and Q fever. The milk must be collected under clean conditions, preferably by

[2]Usually, water is not acceptable for drinking if coliform bacteria exceed 4/100 ml in more than 5% of water samples per month using the membrane-filter technique; samples should be taken at points representative of the distribution system.[104]

automated machines that avoid human contamination, and its quality in the raw state and after pasteurization must meet bacteriological standards.[3] Common pasteurization procedures are heating to 65°C (149°F) for 30 min or the high-temperature or flash method at 72°C (162°F) for 15s. The heat inactivation of the enzyme alkaline phosphatase, normally present in milk, provides the basis for the phosphatase test to ensure proper pasteurization. Before and promptly after pasteurization, milk must be stored and transported at 5–10°C (41–50°F) to storage areas or the consumer. The pasteurization process, even if performed correctly, may not decontaminate some intracellular organisms and those that are cold tolerant, such as *Listeria*. Milk and other food products may contain antibiotics used in treatment of cattle or for growth promotion and pose a hazard to highly sensitive persons.

Our food supplies must also be properly grown, cultivated, stored, and prepared. In developing and tropical areas, vegetables such as lettuce and other products grown in soil enriched by human excreta pose a serious hazard for intestinal infections, and these foods should be avoided by wary travelers. Our modern supermarkets are now selling foodstuffs of all types that have been rapidly imported from other countries and that may carry pathogens. In the summer months, 75% of many fruits and vegetables are harvested outside the country and delivered within days to grocery stores and restaurants in the United States.[105] Salad bars, now present in most restaurants, provide fruits and vegetables that may have originated in Mexico, Central America, or tropical or semitropical climes and are a major source of food poisoning.[106] The fast-food chain, particularly those serving undercooked hamburgers, have been the source of food outbreaks, particularly due to *E. coli* O157:H7 infection in the United States[107]; this organism has also led to an epidemic in a child care center. Foodborne outbreaks have also been due to shigellosis on a commercial airline,[108] and to *Salmonella* in a multistate outbreak due in contaminated cheese.[109] These developments have led to a changing epidemiology of foodborne disease and to new approaches to prevention.[110,111] Human handling during preparation may result in contamination by many bacteria, especially staphylococci, *Salmonella*, and *Shigella*. Thorough cooking immediately prior to eating will reduce the hazard of infection but may fail to inactivate preformed heat-stable toxins such as *C. perfringens*. Proper refrigeration or freezing of food has been as important as water and sewage management in the reduction of intestinal diseases. It prevents the multiplication of most bacteria, and freezing often destroys some parasites such as *Toxoplasma gondii* and *Trichinella spiralis*. However, most organisms or toxins already present at the time of refrigeration or freezing will be preserved in the process and can multiply after thawing and reaching the proper temperature.

[3]Under 200,000 bacteria/ml by standard plate count before pasteurization and under 30,000 bacteria/ml after pasteurization.

14.1.5. Animals and Insect Vectors. Animals provide the source of infection for many of the diseases discussed in this book, such as anthrax, brucellosis, *Campylobacter* infection, leptospirosis, plague, salmonellosis, tularemia, and yersiniosis. The types of exposure differ: some are occupational (anthrax) or avocational (tularemia), some result from common environmental exposures (leptospirosis, salmonellosis), some from close contact with domestic animals (*Campylobacter*), or some from contamination of water sources (*Campylobacter*, yersiniosis) by animals. Knowledge of these potential sources of infection and of appropriate specific measures to avoid or minimize exposure is needed.

Insect vectors may play a passive or active role in transmission of bacterial infections. Passive transfer of the organisms of cholera, salmonellosis, and typhoid fever by flies and other insects may occur but does not seem to be of much epidemiological significance. Good food sanitation, proper storage, and screens are useful to prevent such transfer. The active transport of infection involves multiplication in the insect host. Rickettsial infections are commonly transmitted by insect vectors: *R. rickettsii* of Rocky Mountain spotted fever by wood, dog, and lone star ticks; *R. akari* of rickettsialpox by the mouse mite; and *R. prowazekii* of typhus fevers by the body louse (louse-borne typhus) or rat flea (murine typhus). *B. burgdorferi*, the spirochete that causes Lyme disease, is transmitted by ticks of the *Ixodid* genus, such as *I. dammini*, the deer tick in eastern and midwestern states, and by *I. pacifus* in western states. Ticks may also transmit ehrlichiosis (Sennetsu fever) and babesiosis, and cases have been recognized in the eastern United States.

The control of many of these insect vectors is very difficult, since they exist widely in nature and in many domestic gardens and lawns in endemic areas. Careful protection of the body, especially wearing long pants and high stockings, along with an antitick insecticide in summer months in outside work is important in prevention of tick bites. Intensive searching of the body, as well as domestic pets, after potential exposure is important in preventing Lyme infection, since the tick must remain on the skin some 24 h before it can transmit the organism. Attention should also be directed at the control or avoidance of the dog, rat, mouse, deer, or other animal hosts on which the ticks usually reside. The body louse is controlled by good personal and clothing hygiene and by delousing procedures (heat and chemical treatment).

14.2. Host Factors

The human host may be protected against infection and disease by quarantine or isolation from the sources of infection, by good personal hygiene (especially hand washing), by specific immunization, and by chemoprophylaxis.

14.2.1. Quarantine and Isolation. Quarantine, which began around 1,348 as a 40-day period of keeping suspected plague victims aboard ships or in house quarantine in Venice, has now been rendered largely obsolete by air travel. The WHO now evokes quarantine measures only for plague, yellow fever, and cholera. We rely on surveillance techniques, as discussed in Chapter 2 and by Teutsch,[16] to provide constant monitoring and analysis of infectious diseases and of other conditions of public health importance. The emergence of new and antibiotic-resistant infectious agents[10] has alerted us to the deficiencies in our current surveillance system in the United States,[112] as well as in Europe.[15] A prevention and surveillance strategy has been developed by the CDC for these emerging infections.[96]

Isolation requirement and techniques have also undergone redefinition and reassessment (see Chapter 25 and recent books for details).[113,114] Varying isolation standards in hospitals have been developed for various groups of diseases and often depend on state laws or hospital regulations. Infectious diseases in hospitals have been grouped according to the degree of isolation recommended. Standard precautions are recommended for all patients regardless of their diagnosis. Specific precautions, "transmission-based precautions," are recommended for specific situations. Hand washing remains as a recommendation following any patient contact.

Standard precautions are now legally mandated based on the assumption that the blood and certain body fluids (amniotic fluid, pericardial fluid, peritoneal fluid, pleural fluid, cerebrospinal fluid, semen, vaginal secretions, and any body fluid visibly contaminated with blood) are potentially infected, irrespective of the patient from whom it is derived. With this in mind, the CDC has issued recommendations for the prevention of transmission of HIV, hepatitis B, and other blood-borne pathogens in medical care settings.[115] These standard precautions are to be applied to all patients, including those coming into emergency rooms, where there is often risk of such exposures and the status of the patients is usually unknown. The approach also applies to outpatient settings that involve handling of blood or body fluids. Standard precautions specifically involve the use of gloves whenever contact with blood or other such body fluids is anticipated and other barrier techniques (masks, gowns, and protective eyewear) whenever splashes of such fluids are expected. This would apply to the use of gloves when touching blood and body fluids, mucous membranes, or soiled articles or surfaces, and when doing venipunctures or inserting intravenous lines, and to the use of masks in operative or invasive procedures. The decision to initiate routine HIV testing or testing of high-risk patients and high-risk hospital personnel engaged in invasive or other procedures is left to physicians or individual institutions. If such testing is carried out, the CDC outlines the principles of informed consent and confidentiality involved.[116]

14.2.2. Hygiene. High standards of cleanliness of the individual, the family, the food prepared, and the community contribute to the prevention of infectious diseases. The simple measure of thorough and frequent hand washing is of the highest importance in protecting the individual against pathogens and in interrupting the spread of organisms to others. It plays an essential role in controlling the spread of infection in hospitals and institutions, in restaurants, and in food processing both in industries and at home. The promotion, distribution, and proper use of soap and water for personal hygiene in developing countries need greater emphasis. Its use should decrease enteric and respiratory infections.

14.2.3. Immunization. The specific protection of the individual against infection and disease is the key to modern preventive practice. It may be either passive protection by the transfer of a specific antibody (or antitoxin) from another person or animal immune to it or active immunization through induction of antibody by the organism itself or an antigenic derivative of it. An ideal vaccine closely simulates the protection from natural infection, i.e., it produces good humoral, cellular, and local immunity of long duration. Preferably, it should be better than the short-lived or incomplete immunity found in certain infections such as cholera or shigellosis. It should be in a form of administration and at a cost acceptable to the public. The cost of the vaccine and any side effects should be less than those of the natural disease prevented by it. These ideals are most closely met by well-attenuated live vaccines or antigenic derivatives thereof. The live bacterial vaccines include bacille Calmette–Guérin (BCG) for tuberculosis, a recently developed and licensed oral vaccine (using strain Ty21a) for typhoid fever, and tularemia vaccine. BCG is sparsely used in the United States, and controversy exists about its efficacy (see below). Tularemia vaccine is used in rather small, high-risk groups. Most bacterial vaccines are formalin-, acetone-, or phenolkilled organisms or an antigenic derivative such as the capsular polysaccharides of the meningococcus and pneumococcus (23 types), the toxoids of diphtheria and tetanus, or the protein antigens of *B. anthracis*.

Newer or improved vaccine preparations for many bacterial diseases are under development, testing, or licensure such as those for cholera, *H. influenzae* type b

conjugate (now licensed and used) pertussis, shigellosis, and typhoid fever. The use of conjugated polysaccharide vaccines improves their antigenicity, permitting them to be used in young children.

Someday, timed-release biodegradable polymers may permit pulsed release of vaccines, such as tetanus, thus permitting a single shot to be effective, and avoid the loss now occurring in women and children who do not return to complete the multiple doses required for most killed vaccines. The Institute of Medicine of the U.S. National Academy of Sciences has published a comprehensive evaluation of vaccine priorities for both developed and developing countries based on their feasibility, cost, need, effectiveness, acceptability, side reactions, and other factors.[117]

In developing countries, the WHO's Expanded Program in Immunization is making an enormous effort to vaccinate the young children of the world against six targeted diseases using diphtheria–pertussis–tetanus (DPT), polio, measles, and BCG vaccines, as well as hepatitis B and yellow fever vaccine in some regions. Important progress is being made, and the worldwide coverage in 1996 was approximately 70%. Other organizations are now joining in this effort, as part of a "Child Survival Program," and there is a focus on "growth, oral rehydration therapy, breast feeding, and immunization" (GOBI). The Children's Vaccine Initiative, the organization that manages the technological transition toward new vaccines, has outlined the desired characteristics of such vaccines and has stated that they should be capable of being given orally in the first year of life. In the United States, the recommendation by states that all children be immunized before being allowed into school has greatly expanded coverage in this country. Of the nine diseases against which children are routinely vaccinated, the reported number for five of these and for congenital rubella syndrome was at or near the lowest levels ever.[118] The reported number of these five diseases in 1996 were diphtheria (2 cases), measles (508 cases), poliomyelitis (wild virus—0 cases), rubella (238 cases), and tetanus (36 cases). Only seven cases of congenital rubella syndrome were reported. Measles is a good example of the progress made. After an outbreak of measles between 1989 and 1991 that involved more than 50,000 cases and 11,000 hospitalizations, reported cases declined from 9,643 cases in 1991 to only 281 in 1993.[118,119] Rapid progress is being made in the reduction of meningitis caused by type b *H. influenzae* due to the widespread use of Hib vaccines.

In a survey in 1987, however, serious vaccine deficiencies were found in adults.[120] For example, sero-surveys indicated that 49–66% of persons 60 years or over lacked reliable protective levels of circulating antitoxin against tetanus, and 41–84% lacked adequate protection against diphtheria. Tetanus is a completely preventable disease, and persons over 50 account for 70% of reported cases; thus, special emphasis must be placed on this age group for tetanus boosters, or an initial series if not previously vaccinated. Pneumococcal vaccine is also badly underutilized as indicated by the fact that less than 10% of the higher-risk groups have been vaccinated. A similar lack of protection of our adult population exists against many viral diseases, especially influenza, measles, mumps, rubella, and hepatitis B, as well as pneumonia. Today, some 50,000–70,000 adults die each year of influenza, pneumococcal infections, and hepatitis B, with a cost to society of these and other vaccine-preventable diseases of adults exceeding 10 billion dollars each year.[121] Detailed recommendations have been issued to improve this situation[121] and a call for action issued by the CDC.[122]

Recommendations for the immunization of persons with altered immunocompetence, such as AIDS, have been made by the Advisory Committee on Immunization Practice (ACIP). In general, live viral or bacterial vaccines are contraindicated in persons with severe immunodeficiency due to any cause, including HIV-infected persons. However, evaluation and testing for HIV infection of asymptomatic persons are not necessary before administering measles–mumps–rubella (MMR) vaccine, since no documented serious adverse reactions have been noted in either asymptomatic or symptomatic persons infected with HIV. Thus, MMR vaccine is recommended for both adults and children when otherwise indicated, regardless of HIV status. Enhanced, inactivated poliomyelitis vaccine is preferred in HIV-infected persons, as is pneumococcal vaccine of these persons over age 2 years. HIV-infected children under 2 years should receive Hib vaccine according to the routine schedules. Both HIV-infected children may have suboptimal immune responses to such vaccines. Recent studies suggest, however, that the benefits of measles, mumps, and rubella vaccines outweigh the risks to children with AIDS, at least in developing countries. It should be noted that in developing countries where the risks of exposure are higher, greater use of live vaccines is recommended. The WHO thus recommends use of standard Expanded Programme on Immunization (EPI) vaccines in persons with symptomatic or asymptomatic HIV infections,[123] but suggests that inactivated poliomyelitis vaccine (IPV) be considered as an alternative to oral polio vaccine (OPV). Some complications have arisen with BCG vaccine in such immunosuppressed children, and its use should be suspended in unimmunized individuals with symptomatic AIDS in countries where the other targeted diseases remain serious risks; in asymptomatic HIV-infected individuals in areas where the risk of tuberculosis is high, BCG is recommended at birth or soon thereafter. Guidelines should be consulted for updated recommendations, as data are often

incomplete. Separate needles are required to avoid the possibility of parenteral transmission of HIV (and hepatitis B virus). The jet gun should not be used in immunization programs, except in an epidemic emergency, until further data are available on the possible risks associated with its use.

Table 13[124] gives the current recommended schedule for active vaccination of infants and children. Standards for pediatric immunization have also been issued by the same committee.[125] Information for international travelers,[126] as well as the uses and limitations of each vaccine, will be found in the appropriate chapters of this book. A brief summary follows.

14.2.3.1. Anthrax. No confirmed cases reported in the United States since 1988. The vaccine is distributed only by the Division of Biologics, Michigan Department of Public Health, and is intended only for high-risk occupational exposures, such as persons working with imported goat hair, wool, and hides (sheep and goats) and laboratory workers regularly exposed to this organism. The vaccine is a killed cell-free culture filtrate prepared from the protective antigen. A recent review of anthrax is available.[127] (See also Chapter 4.)

14.2.3.2. Botulism. There are three forms: classical, infant, and wound; a total of 119 cases were reported in 1996. Passive immunization is available consisting of horse serum with anti-A, B, and E toxins and used for persons strongly suspected of botulism or when disease is first diagnosed. Trivalent antitoxin is available from the CDC in Atlanta.

Table 13. Recommended Childhood Immunization Schedule, United States, 1997[a]

	Age										
Vaccine	Birth	1 mo	2 mos	4 mos	6 mos	12 mos	15 mos	18 mos	4–6 yrs	11–12 yrs	14–16 yrs
Hepatitis B[b,c]	Hep B-1		Hep B-2		Hep B-3					*Hep B*[c]	
Diphtheria, and tetanus toxoids and acellular pertussis[d]			DTap or DTP	DTap or DTP	DTap or DTP		DTap or DTP		DTap or DTP	Td	
Haemophilus influenzae type b[e]			Hib	Hib	Hib	Hib					
Poliovirus[f]			Polio[f]	Polio			Polio		Polio		
Measles, mumps, rubella[g]						MMR			MMR or MMR		
Varicella virus[h]							Var			***Var***	

[a]This schedule indicates the recommended age for routine administration of currently licensed childhood vaccines. Some combination vaccines are available and may be used whenever administration of all components of the vaccine is indicated. Providers should consult the manufactures' package inserts for detailed recommendations. Vaccines are listed under the routinely recommended ages. Bars indicate range of acceptable ages for vaccination. Shaded bars indicate catch-up vaccination: at 11–12 years, hepatitis B vaccine should be administered to children not previously vaccinated, and varicella virus vaccine should be administered to unvaccinated children who lack a reliable history of chickenpox. Use of trade names and commerical sources is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services. Source: Advisory Committee on Immunization Practices (ACIP), American Academy of Pediatrics (AAP), and American Academy of Family Physicians (AAFP).

[b]*Infants born to hepatitis B surface antigen (HBsAg)-negative mothers* should receive 2.5 μg of Merck vaccine (Recombivax HB®) or 10 μg of SmithKline Beecham (SB) vaccine (Energix-B®). The second dose should be administered >1 month after the first dose. *Infants born to HBsAg-positive mothers* should receive 0.5 ml hepatitis B immune globulin (HBIG) within 12 h of birth and either 5 μg of Merck vaccine (Recombivax HB®) or 10 μg of SB vaccine (Engerix-B®) at a separate site. The second dose is recommended at age 1–2 months and the third dose at age 6 months. *Infants born to mothers whose HBsAg status is unknown* should receive either 5 μg of Merck vaccine (Recombivax HB®) or 10 μg of SB vaccine (Engerix-B®) within 12 h of birth. The second dose of vaccine is recommended at age 1 month and the third dose at age 6 months. Blood should be drawn at the time of delivery to determine the mother's HBsAg status; if it is positive, the infant should receive HBIG as soon as possible (no later than age 1 week). The dosage and timing of subsequent vaccine doses should be based on the mother's HBsAg status.

[c]Children and adolescents who have not been vaccinated against hepatitis B during infancy may begin the series during any childhood visit. Those who have not previously received three doses of hepatitis B vaccine should initiate or complete the series at age 11–12 years. The second dose should be administered at least 1 month after the first dose, and the third dose should be administered at least 4 months after the first dose and at least 2 months after the second dose.

[d]Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) is the preferred vaccine for all doses in the vaccination series, including completion of the series in children who have received one or more doses of whole-cell diphtheria and tetanus toxoids and pertussis vaccine (DTP). Whole-cell DPT is an acceptable alternative to DTaP. The fourth dose of DTaP may be administered as early as 12 months of age, provided 6 months have elapsed since the third dose and if the child is considered unlikely to return at age 15–18 months. Tetanus and diphtheria toxoids (Td), absorbed, for adult use, are recommended at age 11–12 years if at least 5 years have elapsed since the last dose of DTP, DTaP, or diphtheria and tetanus toxoids. Subsequent routine Td boosters are recommended every 10 years.

[e]Three *H. influenzae* type b (Hib) conjugate vaccines are licensed for infant use. If PRP-OMP (PedvaxHIB® [Merck]) is administered at ages 2 and 4 months, a dose at age 6 months is not required. After completing the primary series, any Hib conjugate vaccine may be used as a booster.

[f]Two poliovirus vaccines are currently licensed in the United States: inactivated poliovirus vaccine (IPV) and oral poliovirus vaccine (OPV). The following schedules are all acceptable by ACIP, AAP, and AAFP, and parents and providers may choose among them: (1) IPV at ages 2 and 4 months and OPV at age 12–18 months and at age 4–6 years; (2) IPV at ages 2, 4, and 12–18 months and at age 4–6 years; and (3) OPV at ages 2, 4, and 6–18 months and at age 4–6 years. ACIP routinely recommends schedule 1. IPV is the only poliovirus vaccine recommended for immunocompromised persons and their household contacts.

[g]The second dose of measles–mumps–rubella vaccine is routinely recommended at age 4–6 years or at age 11–12 years but may be administered during any visit, provided at least 1 month has elapsed since receipt of the first dose and that both doses are administered at or after age 12 months.

[h]Susceptible children may receive varicella vaccine (Var) during any visit after the first birthday, and unvaccinated persons who lack a reliable history of chickenpox should be vaccinated at11–12 years. Susceptible persons aged≥13 years should receive two doses at least 1 month apart.

There is a 10–15% risk of adverse reactions (anaphylaxis, serum sickness). Botulism toxoid is also available and effective, but because of the rarity of the intoxication, it is recommended only for laboratory workers and others working directly with the toxin. It can be obtained from the CDC. (See also Chapter 6.)

14.2.3.3. Cholera. The available inactivated vaccine offers rather poor protection (about 50%) over a short period (3–6 months); the transmission of infection is not prevented. No country or territory currently requires immunization for entry.[126] However, local authorities may require it, and one dose satisfies such regulations and is valid for 6 months. For persons highly exposed in highly endemic areas, a three-dose primary series is given 1 week to 1 month apart and a booster dose every 6 months. The vaccine is probably not effective against the newly discovered *V. cholera* 039 strain. A number of oral cholera vaccines are under development and testing, some of which contain the *V. cholera* 039-Bengal strain.

14.2.3.4. Diphtheria–Pertussis–Tetanus (DPT) Vaccine (see Table 13). Routine primary immunization with DPT vaccine is given at 2, 4, and 6 months with a fourth dose at 15 months and a booster at 4–6 years before entry into school.[124] Some 20% of adults or more may be unprotected against diphtheria and need either a full primary series or a booster dose of a preparation for adults or children >7 years old (Td). Booster doses of Td are suggested for all adults every 10 years.[121] Local Arthus-type reactions and sometimes systemic immune complex reactions (serum sickness) may occur in hyperimmunized adults. These may be attended by severe head, muscle, and joint aches and fever of about 24 h duration. Corticosteroids may be given orally over 3–5 days, for symptomatic relief. Diphtheria antitoxin should be given to asymptomatic, unimmunized contacts in whom close surveillance is not possible, plus penicillin (600,000 U of the benzathine form or, if sensitive, a 7-day course of erythromycin) and injection of diphtheria toxoid. If close surveillance is possible, the antitoxin can be omitted.

14.2.3.5. Haemophilus influenzae Type b Vaccine (Hib). This infection is an important cause of meningitis in children, particularly those under the age of 5 years, and is now being recognized as important in older persons whose immunity has waned. Two forms of conjugated vaccines are available, and two in combination with DPT. They are given at 2, 4, and 6 months with DPT and OPV and again at 12–15 months when MMR is given. One preparation (PRP–OMP) is not given at 6 months (see Table 13 on routine active vaccination of infants and children). (See also Chapter 16.)

14.2.3.6. Meningococcal Infections. Meningococcal infections can result in epidemics but, in U.S. civilians, most commonly occur as single cases or localized clusters, with a third of the cases occurring in persons 20 years of age or over. Two polysaccharide vaccines are currently available in the United States: a bivalent A-C and a quadrivalent vaccine containing A, C, Y, and W-135 polysaccharides. A single dose of either is adequate to induce serospecific immunity.[32] Routine vaccination is not recommended in the United States because of the relatively low risk of infection and because a good group B antigen is not available. Vaccine usage is recommended as an adjunct to antibiotic chemoprophylaxis for household and other close contacts of persons with meningococcal disease due to serotypes A, C, Y, and W-135. The quadrivalent vaccine is recommended for travelers to endemic areas. The duration of protection is unclear. Side reactions are infrequent and mild, but the safety for pregnant women has not been established. Because of the high risk in military recruits, they have received meningococcal vaccine on entering the services since the early 1970s. Currently, they receive groups A, C, Y, and W-135. (See also Chapter 23.)

14.2.3.7. Plague. The vaccine consists of formalin-inactivated organisms; its efficacy has not been critically evaluated. It should be given only to high-risk groups such as field and laboratory personnel exposed to the organism and possibly to workers in plague enzootic or endemic rural areas where avoidance of rodents, fleas, and wild rabbits is not feasible (agricultural advisors, Peace Corps volunteers, or military personnel on maneuvers).[24] The schedule consists of five injections, with dosage varying with age. In the face of continued exposure, single booster doses at about 6-month intervals are given for two doses, then at 1- to 2-year intervals. Local reactions are common, sterile abscesses are rare, and systemic reactions (fever, headache, and malaise) may occur on repeated injections. (See also Chapter 27.)

14.2.3.8. Pneumococcal Infections. The estimated annual incidence of pneumococcal pneumonia in the United States is 68–260 cases per 100,000 population and of bacteremia is 7–25 per 100,000. Mortality is highest in patients with bacteremia, meningitis, underlying medical conditions, and those over 60 years of age. The currently available pneumococcal polysaccharide vaccine contains purified capsular materials from 23 types of *S. pneumoniae*, which together account for 87% of recent bacteremic pneumonia in the United States. The vaccine is particularly recommended for three groups: (1) adults with chronic diseases, especially of the cardiovascular or pulmonary systems; (2) adults with chronic illnesses specifically associated with an increased risk of pneumococcal infection or its complications (splenic dysfunction, Hodgkin's disease, multiple myeloma, cirrhosis, alcoholism, renal failure, CSF leaks, and in immunosuppressed patients); and (3) older adults, especially those 65 years of age and over, regardless of whether they are healthy or diseased. Vaccination is recommended

for hospitalized patients in these high-risk groups before discharge. A single dose is recommended without a booster. Mild side reactions consisting of erythema and pain at the site of injection occur in about half the recipients. Medicare helps pay the cost in these designated groups. Pneumococcal infections are also a problem in young children in developing countries, so that there is increasing interest in the use of the vaccine in these groups. (See also Chapter 28.)

14.2.3.9. Tetanus. See DPT (see Section 14.2.3d) for routine immunization. For wound management, tetanus–diphtheria (Td) adult-type, or tetanus toxoid (TT) only, is used alone or in combination with tetanus immune globulin (TIG) in doses of 250 U (in separate site and syringe), depending on the severity of the wound and the history of prior immunization. Moderate to severe local and systemic reactions may occur in some hyperimmune adults receiving booster doses or for wound prophylaxis. (See also Chapter 37.)

14.2.3.10. Tuberculosis. This disease remains the most important cause of death in the world due to an infectious agent. It is a major killer of individuals in persons aged 20–30 years. In 1994, the WHO declared this disease to be a public health emergency,[128] and it is believed to be "out of control" in many parts of the world. The WHO identified 10 industrial countries in which cases of tuberculosis increased 5–33% in recent years. In the United States, an estimated 15 million persons are believed to be infected. The increase of infection in HIV-infected persons with the emergence of multidrug-resistant strains in this group and in others who were inadequately treated is of special concern. Such resistant strains spread readily to others. About 4.5% of tuberculosis in the United States was associated with HIV infection, and a rise to 13.8% is anticipated by the year 2000. As Comstock[129] has pointed out, the patterns of change and reasons for it are multiple and complex both in the United States and other areas of the world. While HIV is widely blamed, there are many other factors such as migration, poverty, malnutrition, and decreased tuberculosis control efforts, and it is difficult to assess the relative importance of each in the trends observed. In 1991, 56% of active cases were reported among Hispanics and African Americans. The only vaccine available is BCG, and contradictory evidence exists as to its efficacy. An excellent brief review has recently summarized the evidence.[130] More people have received BCG vaccine than any other vaccine, yet its efficacy remains in doubt. It is a part of the routine WHO EPI program. For example, the WHO estimates that 85% of all children born in 1990 received BCG vaccine in their first year of life. Estimates of its efficacy range from 0 to 80% in different settings. Such great variation has been attributed to different vaccine strains, methodological differences, variation in the infecting organism in different countries, the genetic background of the exposed groups, and environmental interactions with other mycobacterial strains in the population. Indeed, a higher efficacy has been seen against leprosy than tuberculosis in some studies. One recent meta-analysis involving 14 trials and 12 observational studies concluded that BCG reduced the risk of tuberculosis by 50%,[131] despite great heterogeneity in the data. In another meta-analysis of results showing homogeneity, BCG was 86% effective against miliary tuberculosis and tuberculous meningitis; the preventive effect against pulmonary tuberculosis showed such heterogeneity that they did not calculate a summary measure.[132] It seems reasonable to believe that BCG is effective against the spread of tuberculosis within the body, such as miliary spread and spread to the meninges, but that its protection against infection varies greatly in different settings and with different vaccines. Comstock[129] has discussed the use of BCG and the CDC has outlined its use in control in a joint statement with the ACIP and the Advisory Committee on the Control of Tuberculosis.[133] General problems in the production standards for BCG and the need for recombinant technology in the development of a vaccine whose mechanism of action and efficacy can be better understood and evaluated have been recently presented.[134–136] BCG use is not routinely recommended in the United States because of the generally low incidence of disease and because BCG interferes with the interpretation of the tuberculin skin test. These recommendations may have to be modified for high-risk groups, in view of recent increases in incidence and resistant organisms. (See also Chapter 39.)

14.2.3.11. Typhoid. Not recommended for routine use in the United States or for international travel except for areas where there is a recognized risk of exposure to *Salmonella typhi*. It is recommended for travelers who will have prolonged exposure to potentially contaminated food and water in smaller cities or villages in rural areas in Africa, Asia, and Central and South America. An oral, live attenuated vaccine is licensed containing the Ty21a strain. It is taken in an enteric-coated capsule on alternate days for four doses, with a booster dose every 5 years if exposure continues.[137] An inactivated parenteral vaccine is also available and soon a Vi capsular polysaccharide vaccine will be available. Few reactions are due to the oral vaccine, but local and systemic reactions lasting 1–2 days are common with the inactivated parenteral vaccine. (See also Chapter 42.)

14.2.4. Antibiotic Prophylaxis. The success of preventing natural infection or disease or both with antibiotic prophylaxis depends on the sensitivity of the organism to the drug employed, whether single or multiple bacterial species are involved, the timing of administration in relation to infection, and the ability of the drug to reach effective concentrations in body sites before the organism is present. It has

Table 14. Prophylactic Uses of Antibiotics

Condition	Chapter (section) in this volume	Persons at risk	Antibiotic	Dose/time
Diphtheria	13(9)	Carriers of toxigenic strains	Penicillin or erythromycin	Full dose over 7–10 days
Gonorrhea	15(9)	Persons sexually exposed to infection	Penicillin	Full dosage as for treatment
Meningococcal meningitis	23(9)	Intimate contacts of cases or in closed outbreaks	Sulfadiazene for sensitive organisms	1 g adults or 0.5 g children q 12 h × 4 doses
			Rifampin	10 mg/kg per day for 4 days
Strep and rheumatic fever	34(9)	Rheumatic heart disease patients (prevention of rheumatic fever)	Penicillin (benzathine), i.m.	1.2 million U/mo
		Sometimes family contacts of strep cases	Penicillin, oral	200,000–250,000 U daily
Surgical infections	25(9.2.8)	Certain surgical patients[a]	Dependent on site of operation	
Syphilis	35(9)	Known exposures ("epidemiological treatment")	Penicillin	Same as treatment
Tuberculosis	39(9.3)	Recent skin test positive Contacts of cases Healed Tb patients; never treated Tb cases	INH	Adults 5 mg/kg per day for 12 mo

[a]C-V, C-section and vaginal hysterectomy, prophylactic hip, certain intestinal, biliary, CNS.

been employed in persons at high risk after known exposure in epidemics (meningococcus), in household contacts of cases (e.g., streptococcus, meningococcus, tuberculosis), and in sexual partners (gonococcus, syphilis), one of whom is infected. It has been employed after infection is diagnosed to prevent further spread or to limit complications (tuberculosis, rheumatic fever) or to limit the duration of the carrier state. The major limitations have been the development of antibiotic resistance, multiple organisms causing the disease, and poor patient compliance for long-term prophylaxis. Any mass prophylactic program aimed at a large group, especially a closed population, over a long term sets the stage for the development of resistance in the organism of interest as well as other circulating organisms. Antibiotic prophylaxis has met with debatable success when the bacterial sensitivity is not high, if the antibiotic is inhibitory but not bactericidal, if multiple organisms are involved (especially gram-negative), and if the risk of infection is relatively low, as in clean surgical operations. For greater detail, see books on clinical infectious diseases[38] or reviews on antibiotic usage,[138] as well as specific chapters in this book.

Table 14 lists some uses of antibiotic prophylaxis. The most successful are the prevention of recurrent streptococcal infections in persons with rheumatic heart disease and the prevention of disease in persons with infections due to *M. tuberculosis*, especially recent infections. Antibiotic prophylaxis with sulfadiazine for sulfa-sensitive organisms or rifampin for sulfa-resistant organisms is advocated for family or close contacts of patients with meningococcal meningitis or outbreaks in closed settings. These principles apply in large community outbreaks when sulfadiazine is given on a mass basis for sulfonamide-sensitive meningococci; of resistant strains in this situation, rifampin is not recommended because of the possibility of developing resistance to this drug.[17] "Epidemiological treatment" after known sexual exposure to gonorrhea or syphilis is effective, but requires a full therapeutic regimen. Prevention of infection during and after surgery is advocated in surgical procedures at high risk to infection such as total hip and knee replacement, colon–rectal surgery, and transurethral resection of the prostate.[139] Patients whose immune status is compromised by steroids, irradiation, alkylating and antimetabolic agents, and other immunosuppressive drugs are at high risk to certain bacterial, fungal, and viral organisms, including some that are not normally pathogenic, but no antimicrobial prophylaxis has been effective. They may be placed in protective isolation (see Section 14.2.1) and closely watched and antibiotic therapy instituted if infection occurs. A possible exception to the ineffectiveness of antibiotics in preventing infections is the prophylactic use of isoniazid in immunosuppressed patients with inactive tuberculosis. Antibiotics or other prophylactic measures for prevention of traveler's diarrhea are recommended only for the long-term traveler in high-risk endemic areas[80,106]; for short-term visitors, bismuth subsalicylate has proved useful.[43]

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