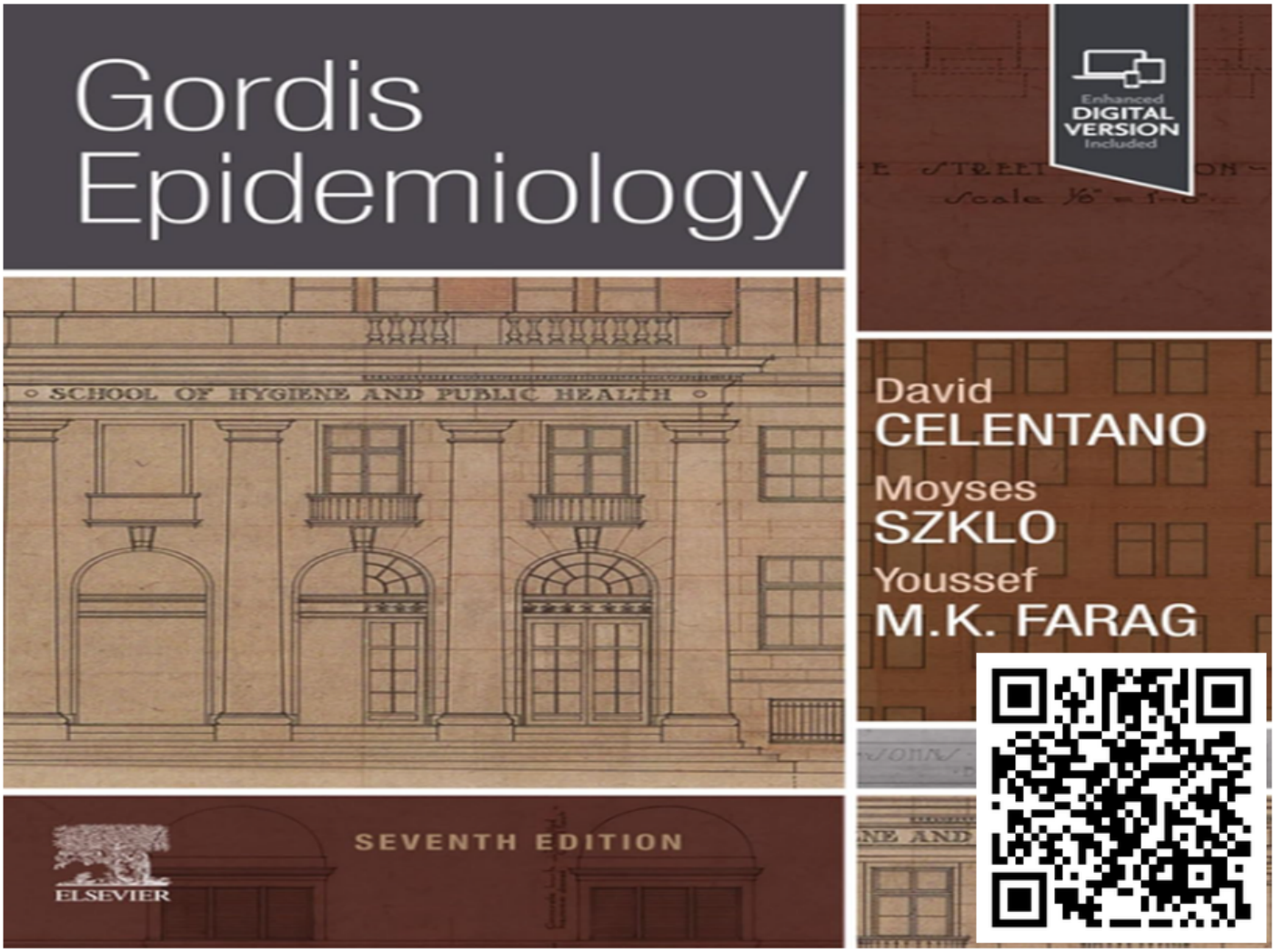

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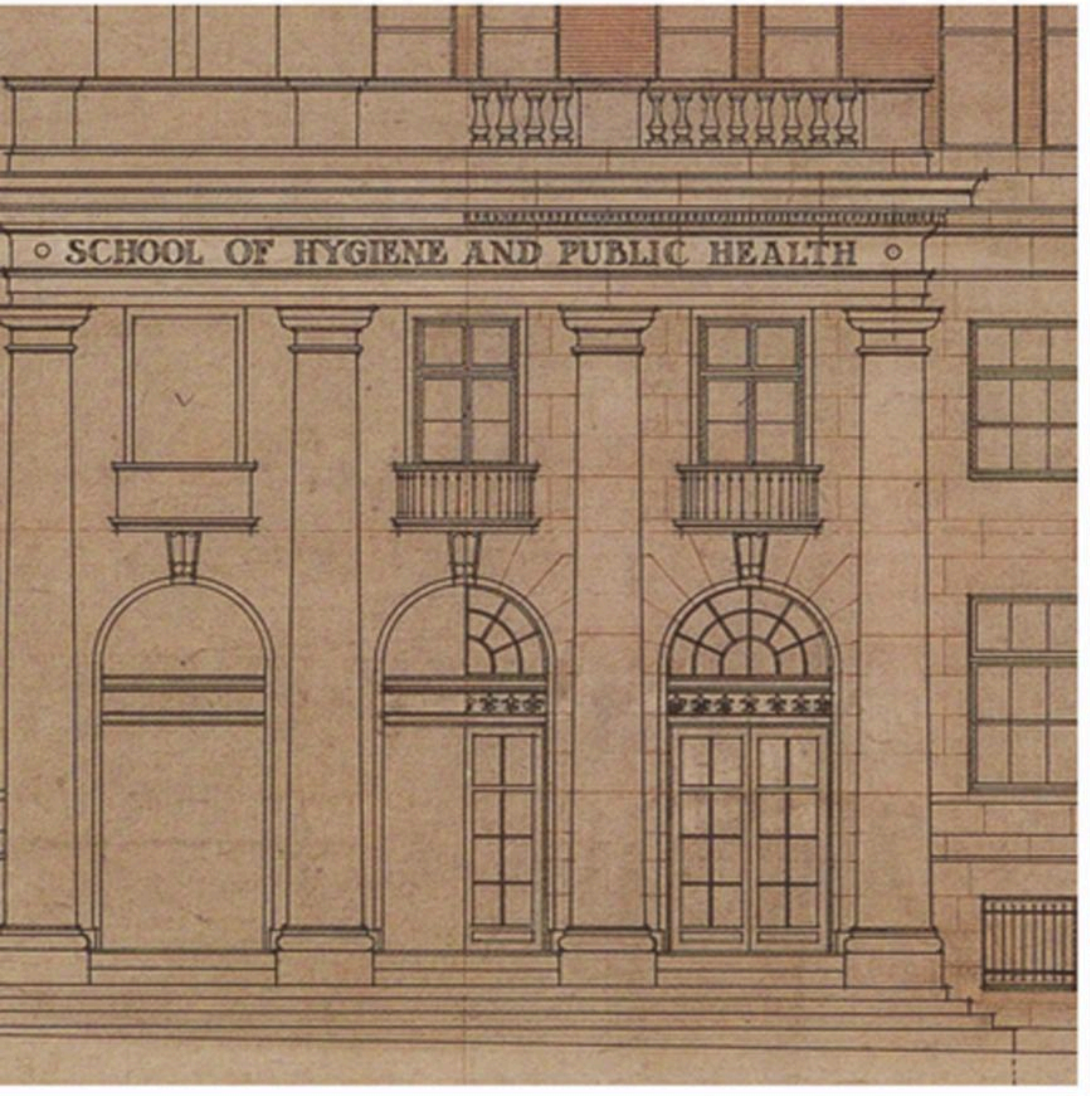

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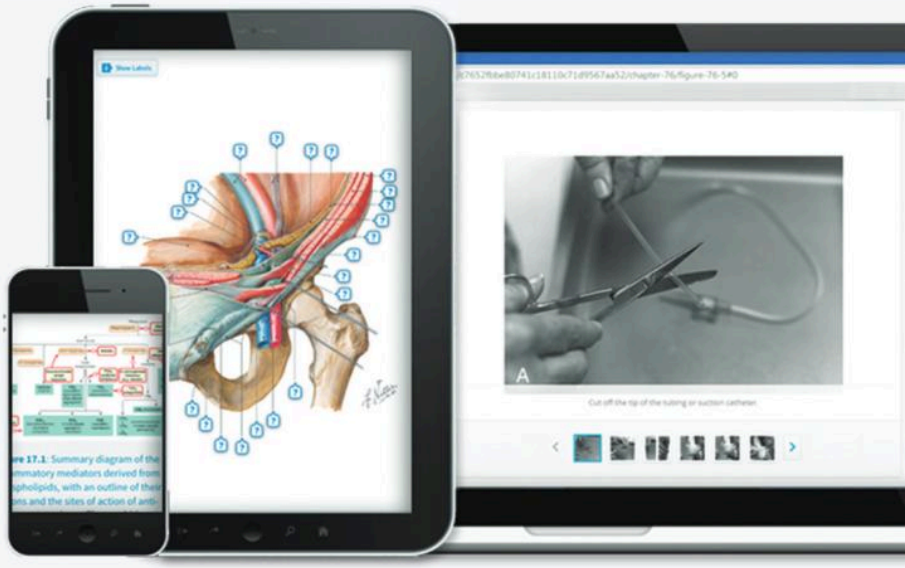

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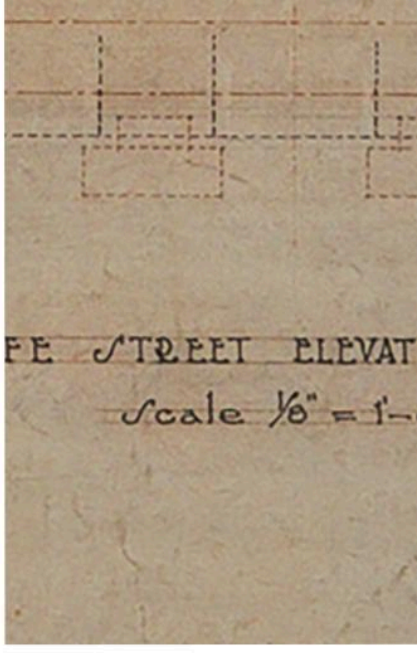

SEVENTH EDITION

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PREFACE

Epidemiology is the foundational discipline underlying public health. Clinical research relies heavily on epidemiologic concepts and methods, and contemporary medical care and health services research, particularly relevant in comparative effectiveness studies and statistical approaches to "big data" (as in the use of the electronic medical record for health studies). As Dr. Leon Gordis wrote in his preface to the fifth edition, "*Epidemiology is the basic science of disease prevention and plays major roles in developing and evaluating public policy relating to health and to social and legal issues*." There are many uses of epidemiology today. Much epidemiologic research focuses on establishing etiologic associations between putative risks and health outcomes. However, epidemiology is also widely used in the evaluation of primary and secondary prevention programs, comparisons of interventions, and the evaluation of policy at the population level. Epidemiologic findings commonly find their way into public media, providing the public and policy makers with data to guide personal decisions regarding their behavior. Think about the SARS-CoV-19 pandemic that swept the world in 2020–2021. The scrutiny focused on epidemiology may cause researchers and practitioners some discomfort, as the interpretation of basic epidemiologic principles can be subject to considerable error. In the contemporary anti-science rhetoric surrounding COVID-19, epidemiology has become a household name while at the same time being derided by some segments of society. Our task in this book is to make the thinking underlying epidemiology transparent.

This text is intended to be a basic introduction to the definitions, logic, and use of epidemiologic concepts and methods to elucidate factors influencing health and disease. We have tried to illustrate the principles with contemporary and historical examples of how epidemiology is applied in the real world. The examples selected include both "classic examples" from the early days of the development of the discipline of epidemiology and contemporary examples such as COVID-19 and monkeypox. Where appropriate, we draw on examples pertaining to clinical practice or health policy.

Upon the passing of Dr. Gordis in 2015, the sixth edition of this book has been revised by two new authors, both of whom worked with and under Professor Gordis and have been actively engaged in teaching epidemiology at Johns Hopkins for over four decades. We have generally retained the structure and organization of the previous edition in this seventh edition. In the fifth edition, learning objectives were inserted in most chapters, and we have revised these and updated the examples throughout. Additional new review questions have been added to most chapters. A significant change in the sixth edition was a reversal of the order of the methods in epidemiology that were previously presented at the end of Section I and more extensively in Section II. Rather than leading with the randomized trial (or the "experimental" design) and then comparing observational study design to the gold standard, we have organized the presentation of epidemiologic methods along a study continuum from clinical observation to case-series to the use of ecologic studies and then to cross-sectional investigations as the foundational approach to epidemiologic hypothesis development. We then follow with case-control and cohort designs, leading up to the randomized trial. This more organically follows the development, in our opinion, of how epidemiologic observations and hypotheses are developed in the daily practice of *doing* epidemiology.

As with the previous edition, the seventh edition consists of three sections. Section I addresses how epidemiology is used to understand health and the development of diseases in populations as the basis for interventions to influence the natural history of disease. The first six chapters provide the conceptual framework underlying the discipline of epidemiology and present many of the basic principles of the discipline. Chapter 1 provides an overview of epidemiology, using many historical examples to illustrate how the field developed in historic context. Chapter 2 is concerned with how disease is transmitted in populations, both directly (in the case of infectious pathogens) and indirectly (for example, through a vector such as a mosquito or contaminated air). The basic terms used in epidemics are presented and illustrated to guide the student in seeing how

these principles and terms are used. Chapter 3 addresses disease surveillance and how we measure morbidity in populations, while Chapter 4 is concerned with aspects of mortality and measures of disease impact in populations. Chapter 5 focuses on ways to detect disease in populations, comparing different approaches to differentiate people who have a disease from those who are disease free, articulating how screening tests can be adjusted to better diagnose those with or those without the disease in question. The issues of the reliability and validity of screening tests are of critical interest to both clinicians and to those planning for health services. Finally, Chapter 6 presents how the natural history of disease can be used to best express disease prognosis, using examples of case-fatality and survivorship.

Section II details the methods used by epidemiologists primarily to ascribe associations between a hypothesized exposure (risk) and a health outcome. Chapter 7 discusses the initial observations made in clinical practice (the case report) leading to a recognition of an accumulation of cases that appear to have some commonalities (the case series). This is followed by an introduction to the ecologic design and its analysis, with cautions as to its interpretation. Finally, cross-sectional (snapshot) studies are presented as the groundwork for hypothesis development. Chapter 8 then introduces observational studies as commonly used in epidemiology, addressing case-control and cohort studies, which are then compared in Chapter 9. To this point, we are addressing exposures as they occur in populations, where we are observers of exposures and their putative impacts on health outcomes. In Chapter 10 we move to the "experimental" approach (randomized trial) in which the investigator "assigns" exposure or health intervention—generally randomly—to study participants to address how this influences the health outcome. In this case the exposure is under the control of the investigator, not the study participant, a crucial difference in the randomized trial as compared to the cohort or other observational study design. Chapter 11 discusses a series of issues involved in the conduct of randomized trials, including sample size, power, and generalizability; determining efficacy (vs. effectiveness); ethical considerations; and the US Federal Drug Administration phases for evaluating new drugs. We added new content in Chapter 11 to describe the context, design, and implications of landmark historical clinical trials. In Chapter 12 we present issues on estimating risk, including absolute and relative risk and their interpretation, calculating and interpreting an odds ratio in a case-control study and in a cohort study, and doing so in a matched-pairs case-control study. In Chapter 13 the concept of risk is expanded to include the calculation and interpretation of the attributable risk, the population attributable risks, and their use in evaluating the success of prevention programs. Causal inference is introduced in Chapter 14 and focuses on how to derive inferences in epidemiologic investigations. Chapter 15 presents issues of bias, confounding, and interaction in epidemiologic studies and discusses how they influence causal inference. Finally, Chapter 16, extensively updated for the seventh edition, addresses the role of genetic and environmental contributions to the etiology of disease and presents new methods of genetic research commonly used in epidemiologic studies today. We also present the amazing growth in genomics research in the past dozen years, and have added a glossary of genetic epidemiology terms to provide the student with some guidance for this somewhat complex field.

Section III addresses the uses of epidemiology in everyday public health. The final four chapters address some of the critical issues facing the field today. Chapter 17 illustrates how epidemiologic principles and designs described in Sections I and II are used in the evaluation of health services. Chapter 18 addresses the use of epidemiology to evaluate screening programs, while Chapter 19 details how epidemiology can be used to address major areas of public health policy. The final chapter summarizes ethical issues confronted in the practice of epidemiology and reviews some of the important professional issues confronted by the field today.

We have continued Professor Gordis' use of illustrations and examples to demonstrate how epidemiologic issues and principles are put into practice. We have updated examples extensively and added new examples throughout the text. Many of the prior chapters have been extensively edited and updated, with some chapters greatly expanded.

Our aim for this book is to allow the reader to appreciate how epidemiology can be used to respond to population health problems confronting society today. Our expectation is not that the reader will be able to conduct an epidemiologic investigation after reviewing this text. Rather, we hope that there will be an appreciation of what epidemiology is, how and why we use basic research and evaluation designs, and how to interpret the

basic findings of an epidemiologic study. We hope that the excitement we feel about the uses of epidemiology will come across to the reader of this text. It took a pandemic for the world to recognize the critical role of epidemiology in our lives!

The cover illustration selected for this edition of *Gordis Epidemiology* has special meaning. The cover is the original architectural rendering of the building supported by the Rockefeller Foundation where the Johns Hopkins School of Hygiene and Public Health was originally housed. Today we continue to inhabit this edifice, where the roots of modern epidemiology developed. While our building today is massively built out, this symbol of the first home of our faculty is sentimental to us where all the authors of this book obtained their doctoral training in public health and epidemiology.

David Celentano
Moyses Szklo
Youssef M.K. Farag
August 2023

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ACKNOWLEDGMENTS

This book reflects the contributions of generations of teachers of epidemiology at Johns Hopkins, first as the School of Hygiene and Public Health with its first class in 1919, and more recently as the Bloomberg School of Public Health. The course was developed by the Department of Epidemiology faculty and was first taught as Principles of Epidemiology by Dr. Abraham Lilienfeld, the chair of the department from 1970 to 1975. Dr. Leon Gordis became the course instructor following an acute illness experienced by Dr. Lilienfeld in the midst of teaching the subject in 1974. Dr. Gordis then was the primary lecturer for the following 30 years. In addition, Dr. Gordis taught epidemiology to cohorts of School of Medicine students at Johns Hopkins at the same time. This book was developed from these experiences, and Dr. Gordis was the sole author of the first five editions of this popular text.

The current authors were all trained in public health and epidemiology at Johns Hopkins and were actively engaged as members of the epidemiology teaching team for many years when they were junior faculty. Dr. Szklo taught the second course in the epidemiology sequence, Intermediate Epidemiology. Upon Jon Samet's departure to University of Southern California in 2008, Dr. Celentano became the chair of the Department of Epidemiology, and the director of Principles of Epidemiology course, which has recently been revised in content and renamed Epidemiologic Inference in Public Health 1. Its content reflects this seventh edition of *Gordis Epidemiology.*

With this edition, we welcome Dr. Youssef M.K. Farag as an author. In the sixth edition, Dr. Farag worked diligently with us in obtaining updated materials, new examples, a thorough review of everything we wrote, and rewriting entire new sections. Dr. Farag is a physician and an epidemiologist. He received his medical degree from Mansoura University Faculty of Medicine in Egypt, and completed his clinical internship in Mansoura University Hospitals, as well as Harvard Medical School affiliated hospitals. He completed a postdoctoral research fellowship at Harvard Medical School, and has an MPH and a PhD in epidemiology from our department at Johns Hopkins Bloomberg School of Public Health where he was recognized by students and faculty and received awards as a gifted teacher of epidemiology over several years. He has richly earned his place on the masthead of this seventh edition!

Many colleagues have made invaluable contributions to this revision of *Gordis Epidemiology.* Chief among them was the late Dr. George W. Comstock, mentor, adviser, and sage scientist to both Drs. Celentano and Szklo. We also acknowledge the assistance of many past and current colleagues, including Haroutune Armenian, our former chair; Jonathan Samet; and Michel Ibrahim, who joined us as professor following his 2002 retirement as dean at the University of North Carolina–Chapel Hill. Others who have had major impacts on the teaching program in the department include Javier Nieto, Rosa Crum, Paul Whelton, Stephen Gange, Shruti Mehta, and Alvaro Munoz. Among prior co-instructors of the introductory course we acknowledge Bill Moss, Elizabeth Platz, Jennifer Deal, and Pablo Martinez Amezcua for their dedication to educating scores of public health students in the "art" of epidemiology. In particular, Dr. Deal has made outstanding contributions to our introductory course, and many of the examples in this edition come from her suggestions. The support of many deans of the school is also appreciated, including the late D.A. Henderson, Al Sommer, Mike Klag, and Ellen MacKenzie. The course on which this book is based would not exist without the long-term dedication and knowledge of our colleague Allyn Arnold who served as the bridge from the Gordis years to the present.

Preparing the seventh edition of this book was a significant undertaking for us. Our goal was to preserve Dr. Gordis' voice—and humor—and to retain the style of the text as much as possible. We also sought to update examples and to intersperse new illustrations of the epidemiologic principles we are presenting along with time-honored classics that were included in earlier editions. Clearly the COVID-19 epidemic gripping the world made clear many of these principles.

The chapter on the role of genetics in contemporary epidemiology was heavily influenced by our genetic epidemiology colleagues Priya Duggal and Genevieve Wojcik. This field has been changing so rapidly—and is

so technologically complicated to the naïve—that they assisted us in doing a major revision in this seventh edition. We cannot thank them enough for their contributions to this chapter.

Preparing the seventh edition of *Gordis Epidemiology* has brought us many memories of Leon and his legacy at Johns Hopkins. The department has certainly changed since he stepped down as chair in 1993. Today we are a significantly larger faculty, numbering 135 full-time faculty in 2022, covering many more areas of epidemiology in greater depth in which there are eight different educational tracks, in addition to a new program in pharmacoepidemiology, and using tools unimaginable even a decade ago. At the same time, the discipline remains grounded in the ideas originally set forth by Wade Hampton Frost at the dawn of our school in 1919. This book is a testament to the thought-leaders and giants of epidemiology who have studied and taught epidemiology at Johns Hopkins over the past 100 years and hopefully will guide us into our second century of practice, education, research, and service.

David Celentano
Moyses Szklo
Youssef M.K. Farag
August 2023

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SECTION I

The Epidemiologic Approach to Disease and Intervention

This section begins with an overview of the objectives of epidemiology, some of the approaches commonly used in epidemiology, and examples of the applications of epidemiology to human health problems (Chapter 1). It then discusses how diseases are transmitted (Chapter 2). Diseases do not arise in a vacuum; they result from an interaction of human beings with their environment, including other people, animals, and the physical environment. An understanding of the concepts and mechanisms underlying the transmission and acquisition of disease is critical to exploring the epidemiology of human disease and to preventing and controlling many infectious diseases.

To discuss the epidemiologic concepts presented in this book, we need to develop a common language, particularly for describing and comparing illness (morbidity) and death (mortality). Chapter 3 therefore discusses morbidity and the important role of epidemiology in disease surveillance. We then present how measures of morbidity are used in both clinical medicine and public health. Chapter 4 presents the methodology and approaches for using mortality data in investigations relating to public health and clinical practice. Other issues relating to the impact of disease, including quality of life and projecting the future burden of disease, are also discussed in Chapter 4.

Armed with knowledge of how to describe morbidity and mortality in quantitative terms, we then turn to the question of how to assess the quality of diagnostic and screening tests that are used to determine who in the study population has a certain disease (Chapter 5). After we identify people with the disease, we need ways to describe the natural history of disease in quantitative terms; this is essential for assessing the severity of an illness and for evaluating the possible effects on survival of new therapeutic and preventive interventions (Chapter 6).

This first section, then, introduces the student to the nomenclature of epidemiology, surveillance and its ramifications for determining the health of populations, and then focuses on screening and the natural history of disease.

1

Introduction

I hate definitions.
—Benjamin Disraeli (1804–1881, British Prime Minister 1868 and 1874–1880)

WHAT IS EPIDEMIOLOGY?

Epidemiology is the study of how diseases or health characteristics are distributed in populations and the factors that influence or determine this distribution. Why does a disease develop in some people and not in others? The premise underlying epidemiology is that disease, illness, ill health, and excellent health status are not randomly distributed in human populations. Rather, each of us has certain characteristics that predispose us to, or protect us against, a variety of different diseases. These characteristics may be primarily genetic in origin, the result of exposure to certain environmental hazards, or the behaviors (good and bad) that we engage in. Perhaps most often, we are dealing with an interaction of genetic, environmental, and behavioral and social factors in the development of disease.

A broader definition of epidemiology than that given previously has been widely accepted. It defines epidemiology as "*the study of the distribution and determinants of health-related states or events in specified populations and the application of this study to control of health problems*."[1] What is noteworthy about this definition is that it includes both a description of the content of the discipline and why epidemiologic investigations are carried out.

Perhaps it is best to go back to the roots of the discipline. Wade Hampton Frost, the inaugural chair of the Department of Epidemiology at the Johns Hopkins School of Hygiene and Public Health. Frost wrote:

> *"For epidemiological description the unit is an aggregation of individuals making up a population, and description of the mass-phenomenon of a disease consists of its types and frequency of occurrence in the population as a whole and in its different component groups."*[2]

This statement was to contrast with the clinical description of disease where "*the unit is an individual, and the phenomenon of the clinical reaction may be described in terms of the character and distribution of anatomic lesions and the nature and sequence of symptoms.*"[2]

OBJECTIVES OF EPIDEMIOLOGY

What are the specific objectives of epidemiology? First, to identify the *etiology,* or *cause,* of a disease and its relevant risk factors (i.e., factors that increase a person's risk for a disease). We want to know how the disease is transmitted from one person to another or from a nonhuman reservoir to a human population or why it arises due to risk behaviors the person engages in. Our aim is to intervene to reduce morbidity and mortality from the disease. We want to develop a rational basis for prevention programs. If we can identify the etiologic or causal factors for disease and reduce or eliminate exposure to those factors, we can develop prevention programs. In addition, we can develop appropriate vaccines and treatments, which can prevent the transmission of the disease to others. However, while we may not always be able to identify *a cause* of a disease, epidemiology can be used to identify the *factors associated with*, but not necessarily causing, the disease. For example, Black individuals are more likely to develop hypertension. The Black race, however, is not causally related to hypertension; this relationship is explained by numerous causes for hypertension that are more common among Black persons, such as obesity and salt intake, which explain

the association. It is, however, useful to know about this noncausal relationship because it allows us to define Black individuals as a high-risk group for hypertension, which should be primarily targeted by preventive programs aimed at reducing associated causes.

The second objective of epidemiology is to determine the *extent of disease* found in the community. What is the burden of disease in the community? This question is critical for planning health services and facilities and for estimating how many future health care providers should be trained.

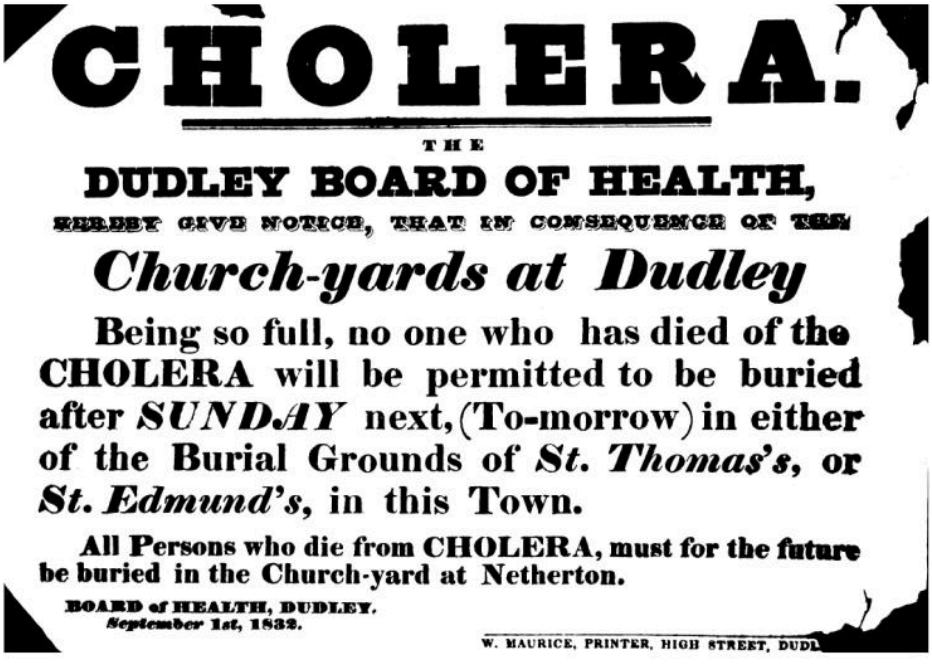
A third objective is to study the *natural history and prognosis of disease*. Clearly, certain diseases are more severe than others; some may be rapidly lethal, whereas others may have extended durations of survival. Many diseases are not fatal, but may affect quality of life or be associated with disability. We want to define the baseline natural history of a disease in quantitative terms so that as we develop new modes of intervention, through programs to prevent the onset of disease, through treatments, or through new ways of preventing complications, we can compare the results of using these new modalities with the baseline data to determine whether our new approaches have truly been effective.

Fourth, we use epidemiology to evaluate both *existing and newly developed preventive and therapeutic measures and modes of health care delivery*. For example, does screening men for prostate cancer using the prostate-specific antigen (PSA) test improve mortality in people found to have prostate cancer? Has the growth of managed care and other new systems of health care delivery and extension of health care insurance had an impact on the health outcomes of those involved and on their quality of life? If so, what has been the nature of this impact and how can it be measured?

Finally, epidemiology can provide the foundation for *developing public policy* relating to environmental problems, genetic issues, and other social and behavioral considerations regarding disease prevention and health promotion. For example, is the electromagnetic radiation that is emitted by cell phones, electric blankets and heating pads, and other household appliances a hazard to human health? Are high levels of atmospheric ozone or particulate matter a cause of adverse acute or chronic health effects in human populations? Is radon in homes a significant risk to human beings? Which occupations are associated with increased risks of disease in workers, and what types of regulation are required to reduce these risks?

Changing Patterns of Community Health Problems

A major role of epidemiology is to provide clues to changes that take place over time in the health problems presenting in the community. Fig. 1.1 shows a sign in a


CHOLERA.

THE

DUDLEY BOARD OF HEALTH,

HEREBY GIVE NOTICE, THAT IN CONSEQUENCE OF THE

Church-yards at Dudley

Being so full, no one who has died of the CHOLERA will be permitted to be buried after *SUNDAY* next, (To-morrow) in either of the Burial Grounds of *St. Thomas's*, or *St. Edmund's*, in this Town.

All Persons who die from CHOLERA, must for the future be buried in the Church-yard at Netherton.

BOARD of HEALTH, DUDLEY.
September 1st, 1832.

W. MAURICE, PRINTER, HIGH STREET, DUDL

Fig. 1.1 Sign in cemetery in Dudley, England, in 1839. (From the Dudley Public Library, Dudley, England.)

cemetery in Dudley, England, in 1839. At that time, cholera was the major cause of death in England; the churchyard was so full that no burials of persons who died of cholera would henceforth be permitted. The sign conveys an idea of the importance of cholera in the public's consciousness and in the spectrum of public health problems in the early 19th century. Clearly, cholera is no longer a major problem in the United States today, but in many low-income and war-torn countries of the world it remains a serious threat, with many countries periodically reporting outbreaks of cholera that are characterized by high death rates, especially in children, often as a result of inadequate or inaccessible medical care and, ultimately, clean sources of water.

Let us compare the major causes of death in the United States in 2019 and 2020 (Fig. 1.2). The categories of causes have been color coded as described in the caption for this figure. In 1900 the leading causes of death were pneumonia and influenza, followed by tuberculosis and diarrhea and enteritis. In 2020 the leading causes of death were heart disease, cancer, coronavirus disease 2019 (SARS Co-V-2), and unintentional injuries.[3] What change has occurred? During the 20th century there was a dramatic shift in the causes of death in the United States. In 1900 the three leading causes of death were infectious diseases; however, now we are dealing with chronic diseases that in most situations are not communicable or largely infectious in origin. Consequently, the kinds of research, intervention, and services we need today differ from those that were needed in the United States in 1900.

The pattern of disease occurrence currently seen in some developing countries is often similar to that which was seen in the United States in 1900: infectious diseases remain the leading causes of death.[4] However, as countries become industrialized, they increasingly manifest the mortality patterns currently seen in developed countries, with mortality from nontransmissible chronic diseases becoming the major challenge (this is commonly referred to as the "epidemiologic transition"). However, even in industrialized countries, as human immunodeficiency virus (HIV) infection and

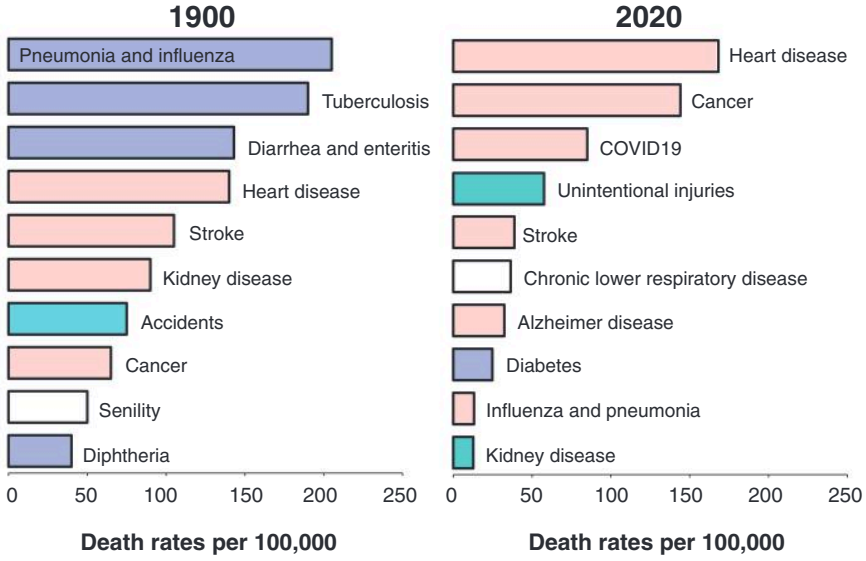


Fig. 1.2 Ten leading causes of death in the United States, 1900 and 2020. Although the definitions of the diseases in this figure are not exactly compare 1900 with 2020, the bars in the graphs are color coded to show chronic diseases *(pink)*, infectious diseases *(purple)*, injuries *(aqua)*, and diseases of aging *(white)*. (Data for 1900 are redrawn from Grove RD, Hetzel AM. *Vital Statistics Rates of the United States, 1940–1960*. Washington, DC: US Government Printing Office; 1968; and Kochanek KD, Murphy SL, Xu JQ, Tejada-Vera B. Deaths: Final data for 2014. *Natl Vital Stat Rep*. 2016;65(4):1–122. [Hyattsville, MD: National Center for Health Statistics.]). Data for 2020 are from Murphy SL, Kochanek KD, Xu JQ, Arias E. *Mortality in the United States, 2020*. NCHS Data Brief, no 427. Hyattsville, MD: National Center for Health Statistics; 2021. Available at: https://dx.doi.org/10.15620/cdc:112079.).

TABLE 1.1 Ten Leading Causes of Death and Their Percentages of All Deaths, United States, 2020

Rank	Cause of Death	Number of Deaths	Percent of Total Deaths	Age-Adjusted Death Rate Per 100,000
	All Causes	33,83,729	100	
1	Heart disease	6,96,962	20.6%	168.2
2	Cancer	6,02,350	17.8%	144.1
3	COVID-19	3,50,831	10.4%	85
4	Accidents (unintentional injuries)	2,00,955	5.9%	57.6
5	Stroke (cerebrovascular diseases)	1,60,264	4.7%	38.8
6	Chronic lower respiratory diseases	1,52,657	4.5%	36.4
7	Alzheimer's disease	1,34,242	4.0%	32.4
8	Diabetes	1,02,188	3.0%	24.8
9	Influenza and pneuomnia	53,544	1.6%	13
10	Kidney disease	52,547	1.6%	12.7

Murphy SL, Kochanek KD, Xu JQ, Arias E. *Mortality in the United States, 2020.* NCHS Data Brief, no 427. Hyattsville, MD: National Center for Health Statistics; 2021. Available at: https://dx.doi.org/10.15620/cdc:112079. Accessed May 08, 2023.

the COVID-19 pandemic have emerged and the incidence of tuberculosis has increased, infectious diseases are once again becoming major public health problems. Table 1.1 shows the 10 leading causes of death in the United States in 2014. The three leading causes—heart disease, cancer, and COVID-19—account for almost 55% of all deaths, an observation that suggests specific targets for prevention if a significant reduction in mortality is to be achieved.

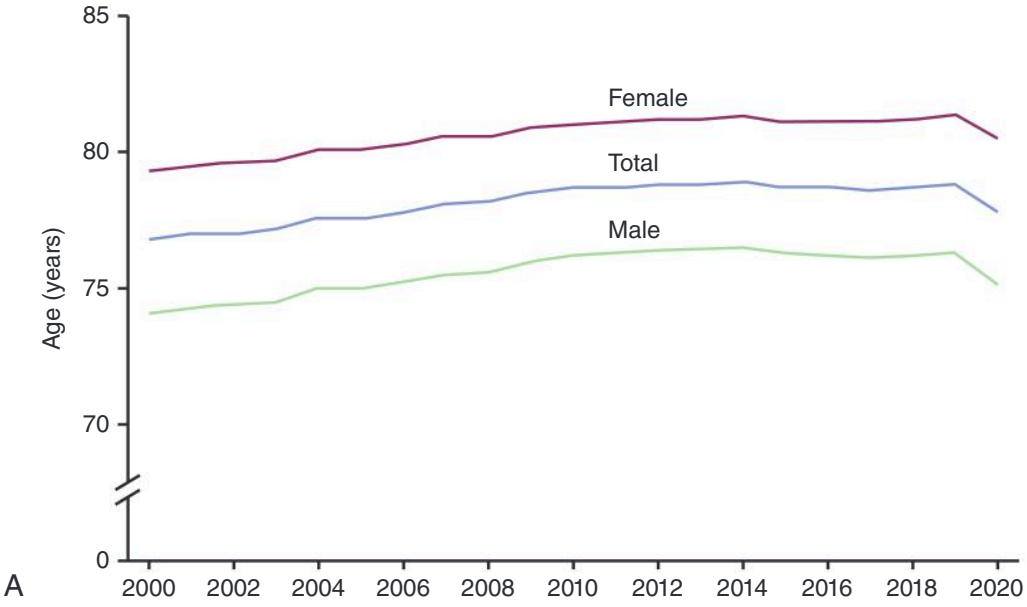
Another demonstration of changes that have taken place over time is seen in Fig. 1.3, which shows the life expectancy at birth by sex between 2002 and 2020 (panel A) and by Hispanic origin and race in 2019 and 2020 (panel B) in the United States.

While the life expectancy has dramatically increased in both sexes over 20 years, most of these public health gains have been swept by the COVID-19 pandemic deaths as we can see from the sharp decline in life expectancy in both sexes and all races.

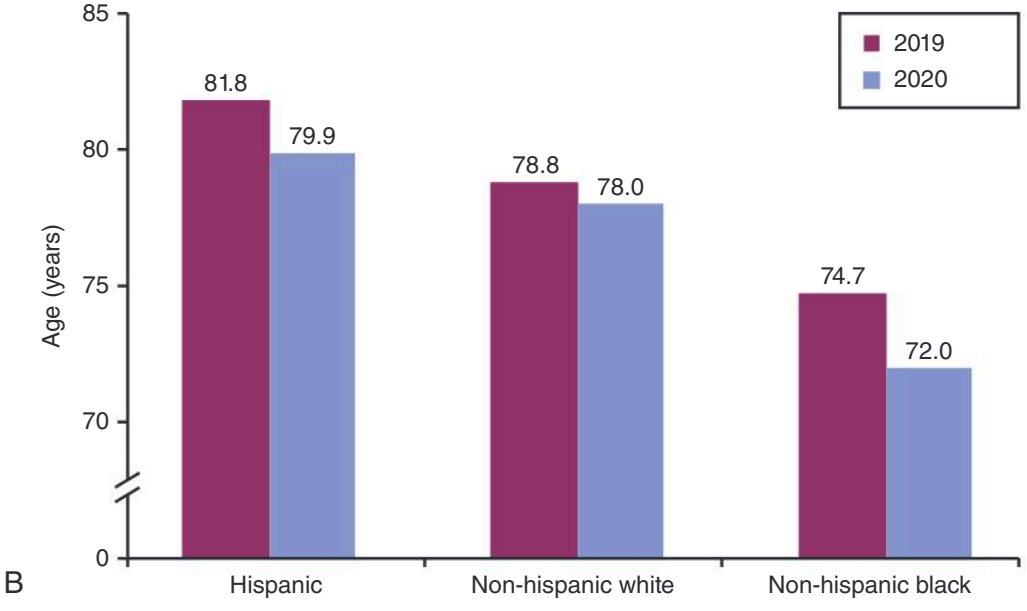
EPIDEMIOLOGY AND PREVENTION

A major use of epidemiologic evidence is to identify subgroups in the population who are at high risk for disease. Why should we identify such high-risk groups? First, if we can identify these high-risk groups, we can direct preventive efforts, such as screening programs for early disease detection, to populations who may not have been screened before and are most likely to benefit from any interventions that are developed for the disease. In sub-Saharan Africa, targeted HIV counseling and testing to men and women who are not aware of their status can effectively reduce epidemics if they are linked to care, started on antiretroviral therapy, and continued in care such that their viral load is undetectable.

Second, if we can identify such groups, we may be able to identify the specific factors or characteristics that put them at high risk and then try to modify those factors. It is important to keep in mind that such risk factors may be of two types. Characteristics such as age, sex, and race, for example, are not modifiable, although they may permit us to identify high-risk groups. On the other hand, characteristics such as obesity, smoking, diet, sexual practices, and other lifestyle factors may be potentially modifiable and may thus provide an opportunity to develop and introduce new prevention programs aimed at reducing or changing specific exposures or risk factors.



Notes: Life expectancies for 2019 by hispanic origin and race are not final estimates; see technical notes. Estimates are based on provisional data from January 2020 through June 2020.
Source: National center for health statistics, National vital statistics system, Mortality data.



Notes: Life expectancies for 2019 by hispanic origin and race are not final estimates; see technical notes. Estimates are based on provisional data from January 2020 through June 2020.
Source: National center for health statistics, National vital statistics system, Mortality data.

Fig. 1.3 **(A)** Life expectancy at birth by sex: United States, 2000–2020. **(B)** Life expectancy at birth by Hispanic origin and race: United States, 2019 and 2020. (From Arias E, Ejada-Vera B, Ahmad F. Provisional life expectancy estimates for January through June, 2020. Vital Statistics Rapid Release; no 10. Hyattsville, MD: National Center for Health Statistics. February 2021.)

Primary, Secondary, and Tertiary Prevention

In discussing prevention, it is helpful to distinguish among primary, secondary, and tertiary prevention (Table 1.2).

Primary prevention denotes an action taken to prevent the development of a disease in a person who is well and does not (yet) have the disease in question. For example, we can immunize a person against certain diseases so that the disease never develops or, if a disease is environmentally induced, we can prevent a person's exposure to the environmental factor involved and thereby prevent the development of the disease. Primary prevention is our goal. For example, we know that most lung cancers are preventable. If we can help to stop people from ever smoking, we can eliminate 80% to 90% of lung and other cancers in human beings. However, although our aim is to prevent diseases from occurring in human populations, for many diseases, such as prostate cancer and Alzheimer disease, we do not yet have the biologic, clinical, or epidemiologic knowledge on which to base effective primary prevention programs.

While the term *primordial prevention* precedes primary prevention, it is not commonly used. *Primordial prevention* denotes the prevention of the exposure to the risk factor of the disease of interest. For example, primordial prevention of hypertension should start in childhood through physical activity, low-sodium diet, no consumption of sugar-sweetened beverages, etc.[5]

Secondary prevention involves identifying people in whom a disease process has already begun, but who have not yet developed clinical signs and symptoms of the illness. This period in the natural history of a disease is called the *preclinical phase* of the illness and is discussed in depth in Chapter 18. Once a person develops clinical signs or symptoms, it is generally assumed that under ideal conditions the person will seek and obtain prompt medical advice. Our objective with secondary prevention is to detect the disease earlier than it would have been detected with usual care. By detecting the disease at an early stage in its natural history, often through screening, it is hoped that treatment will be easier and/or more effective. For example, most cases of early stage breast cancer in older women can be detected through mammography. Several recent studies indicate that routine testing of the stool for occult blood can detect treatable colon cancer early in its natural history, but colonoscopy is a better test, although far more expensive and invasive. The rationale for secondary prevention is that if we can identify disease earlier in its natural history than would ordinarily occur, intervention measures may be more effective and life prolonged. Perhaps we can prevent mortality or complications of the disease and use less invasive or less costly treatment to do so in individuals whose disease is diagnosed at an earlier stage. Evaluating screening for disease and the place of such intervention in the framework of disease prevention are discussed in Chapter 18.

Tertiary prevention denotes preventing complications in those who have already developed signs and symptoms of an illness and have been diagnosed (i.e., people who are in the clinical phase of their illness). This is generally achieved through prompt and appropriate treatment of the illness combined with ancillary approaches, such as physical therapy, that are designed to prevent complications such as joint contractures.

TABLE 1.2 Three Types of Prevention

Type of Prevention	Definition	Examples
Primary	Preventing the *initial development* of a disease	Immunization, reducing exposure to a risk factor
Secondary	Early detection of *existing disease* to reduce severity and complications	Screening for cancer
Tertiary	Reducing the *impact of the disease*	Rehabilitation for stroke

Two Approaches to Prevention: A Different View

Two possible approaches to prevention are a population-based approach and a high-risk approach.[6] In the population-based approach, a preventive measure is widely applied to an entire population. For example, prudent dietary advice for preventing coronary disease or advice against smoking may be provided to an entire population using mass media and other health education approaches. An alternate approach is to target a high-risk group with the preventive measure. Thus, screening for cholesterol in children might be restricted to children from high-risk families. Clearly, a measure

applied to an entire population must be relatively inexpensive and noninvasive or it cannot be thought as cost-effective. A measure that is to be applied to a high-risk subgroup of the population may be more expensive and may be more invasive or inconvenient, but also must be able to correctly identify individuals with the disease. More on screening tests is discussed in Chapter 18. Population-based approaches can be considered public health approaches, whereas high-risk approaches more often require a clinical action to identify the high-risk group to be targeted. In most situations, a combination of both approaches is ideal. Often a high-risk approach, such as prevention counseling, is limited to brief encounters with physicians. These approaches are discussed further in Chapter 19.

Fig. 1.4 "You've got whatever it is that's going around." (Al Ross/The New Yorker Collection/The Cartoon Bank.)

EPIDEMIOLOGY AND CLINICAL PRACTICE

Epidemiology is critical not only to public health but also to clinical practice. The practice of medicine is dependent on population data. For example, if a physician hears an apical systolic murmur, a heart sound produced when blood flows across the heart valves, how does he or she know whether it represents mitral regurgitation? Where did this knowledge originate? The diagnosis is based on correlation of the clinical findings (such as the auscultatory findings—sounds heard using a stethoscope) with the findings of surgical pathology or autopsy and with the results of echocardiography, magnetic resonance, or catheterization studies in a large group of patients. Thus, the process of diagnosis is population based (see Chapter 5). The same holds for prognosis. For example, a patient asks his physician, "How long do I have to live, doctor?" and the doctor replies, "Six months to a year." On what basis does the physician prognosticate? They do so based on experience with large groups of patients who have had the same disease, were observed at the same stage of disease, and received the same treatment. Again, prognostication is based on population data (see Chapter 6). Finally, selection of appropriate therapy is also population based. Randomized clinical trials that study the effects of a treatment in large groups of patients are the ideal means (the so-called gold standard) for identifying appropriate therapy (see Chapters 10 and 11). Thus population-based concepts and data underlie the critical processes of clinical practice, including diagnosis, prognostication, and selection of therapy. In effect, the physician applies a population-based probability model to the patient on the examining table.

Fig. 1.4 shows a physician demonstrating that the practice of clinical medicine relies heavily on population concepts. What is portrayed humorously here is a true commentary on one aspect of pediatric practice—a pediatrician often makes a diagnosis based on what the parent tells them over the telephone and on what they know about which illnesses, such as viral and bacterial infections, are "going around" in the community. Thus, the data available about illness in the community can be very helpful in suggesting a diagnosis, even if they are not conclusive. Data regarding the etiology of sore throats according to a child's age are particularly relevant (Fig. 1.5). If the infection occurs very early in life, it is likely to be viral in origin. If it occurs at ages 4 to 7 years, it is likely to be streptococcal in origin. In an older child, *Mycoplasma* becomes more typical. Although these data do not make the diagnosis, they do provide the physician or other health care provider with a good clue as to what agent or agents to suspect.

EPIDEMIOLOGIC APPROACH

How does the epidemiologist proceed to identify the cause of a disease? Epidemiologic reasoning is a multistep process. The first step is to determine whether a statistical association exists between exposure to a factor (e.g., an environmental agent) or a characteristic of a

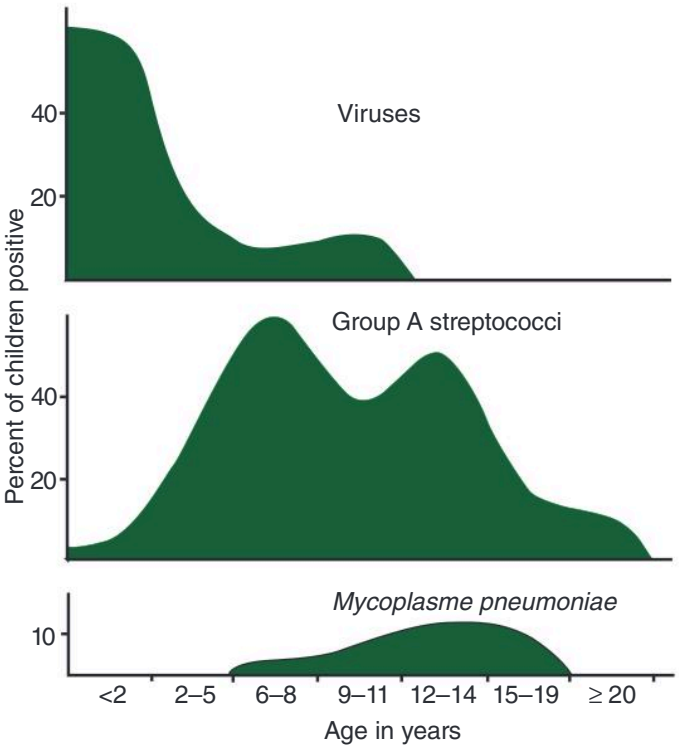


Fig. 1.5 Frequency of agents by age of children with pharyngitis, 1964–1965. (From Denny FW. The replete pediatrician and the etiology of lower respiratory tract infections. *Pediatr Res.* 1969;3:464–470.)

person (e.g., an increased serum cholesterol level) and the presence of the disease in question. We do this by studying the characteristics of groups and the characteristics of individuals.

If we find there is indeed an association between an exposure and a disease, is it necessarily a causal relationship? No, not all associations are causal. The second step therefore is to try to derive appropriate inferences about a possible causal relationship from the patterns of the associations that have been previously found. These steps are discussed in detail Chapter 14.

Epidemiology often begins with descriptive data. For example, Fig. 1.6 shows rates of gonorrhea in the United States and its territories in 2011 and 2020 by state. Clearly, there are marked regional variations in reported cases of gonorrhea. The first question to ask when we see such differences between two groups or two regions or at two different times is, "Are these differences real?" In other words, are the data from each area of comparable quality? Before we try to interpret the data, we should be satisfied that the data are valid. If the differences are real, then we ask, "Why have these differences occurred?" Are there differences in potential exposures between high-risk and low-risk areas, or are there differences in the people who live in those areas? This is where what has been named analytic epidemiology begins its investigation.

Many years ago, it was observed that communities in which the natural level of fluoride in the drinking water varied were related to the frequency of dental caries in the permanent teeth of residents. Communities that had low natural fluoride levels had high levels of caries, and communities that had higher levels of fluoride in their drinking water had low levels of caries (Fig. 1.7). This finding suggested that fluoride might be an effective prevention intervention if it were artificially added to the drinking water supply. A trial was therefore carried out to test the hypothesis. Although, ideally, we would like to randomize a group of people either to receive fluoride or to receive no fluoride, this was not possible to do with drinking water because each community generally shares a common water supply. Consequently, two similar communities in upstate New York, Kingston and Newburgh, were chosen for the trial. The DMF index, a count of decayed, missing, and filled teeth, was used. Baseline data were collected in both cities, and at the start of the study, the DMF indices were comparable in each age group in the two communities. The water in Newburgh was then fluoridated, and the children were reexamined a decade later. Fig. 1.8 shows that, in each age group, the DMF index in Newburgh had dropped significantly 10 years or so later, whereas in Kingston, there was no change. This is strongly suggestive evidence that fluoride was preventing caries.

It was possible to go one step further in trying to demonstrate a causal relationship between fluoride ingestion and low rates of caries. The issue of fluoridating water supplies has been extremely controversial, and in certain communities in which water has been fluoridated, there have been referenda to stop the fluoridation. It was therefore possible to look at the DMF index in communities such as Antigo, Wisconsin, in which fluoride had been added to its water supply and then, after a referendum, fluoridation had been stopped. As seen in Fig. 1.9, after the fluoride was removed, the DMF index rose. This provided yet a further piece of evidence that fluoride acted to prevent dental caries.

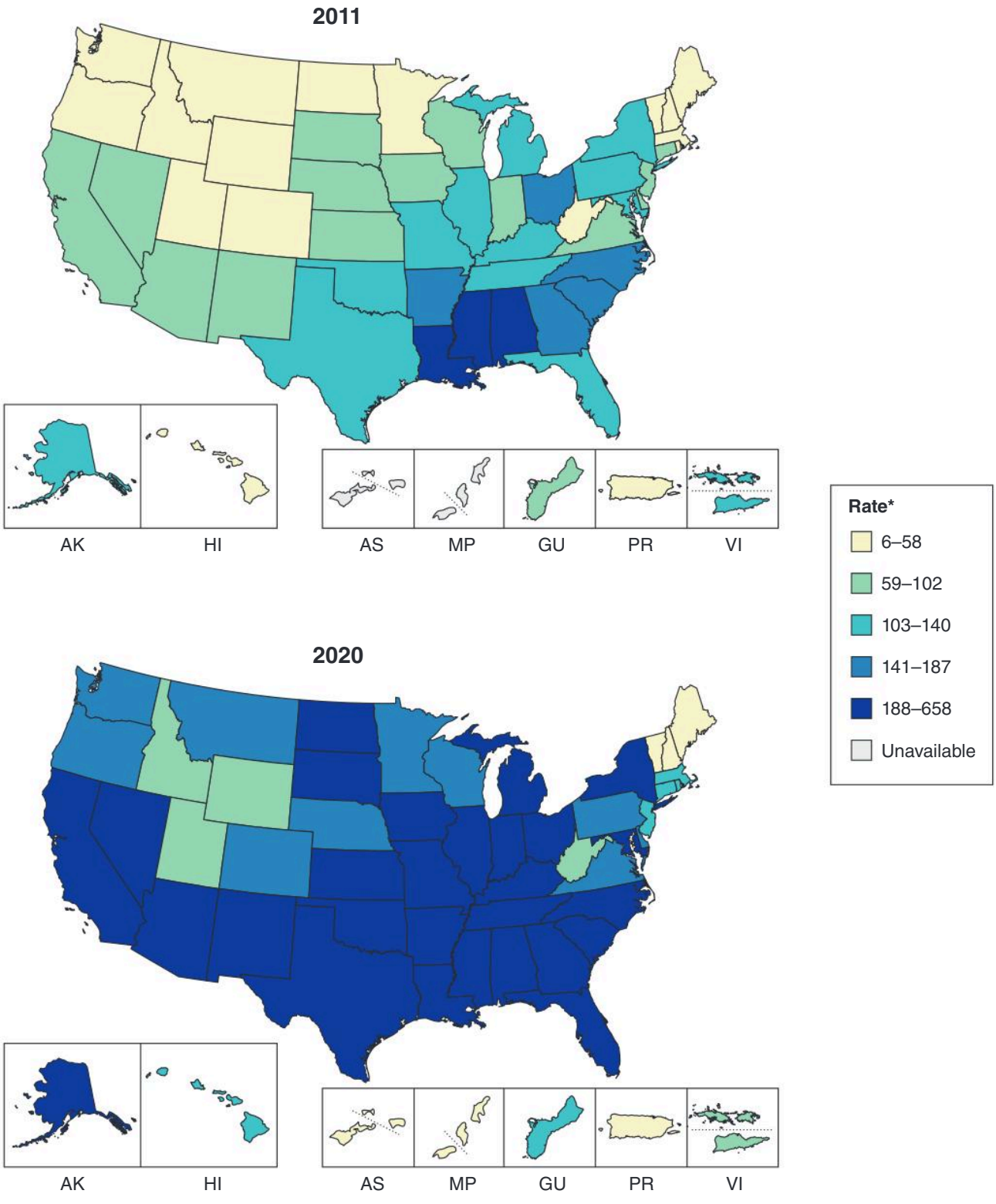


Fig. 1.6 Gonorrhea—rates of reported cases by state, United States and Territories, 2011 and 2020. In 2011, eight states and the District of Columbia (DC; 16.1% of available areas) had a rate of reported gonorrhea greater than or equal to 141 cases per 100,000 population. This increased to 38 states and DC (69.6% of available areas) in 2020. (From Centers for Disease Control and Prevention. National Center for HIV, Viral Hepatitis, STD, and TB Prevention. Division of STD Prevention. Sexually Transmitted Disease Surveillance 2020. https://www.cdc.gov/std/statistics/2020/figures/2020-STD-Surveillance-Gonorrhea.pptx)

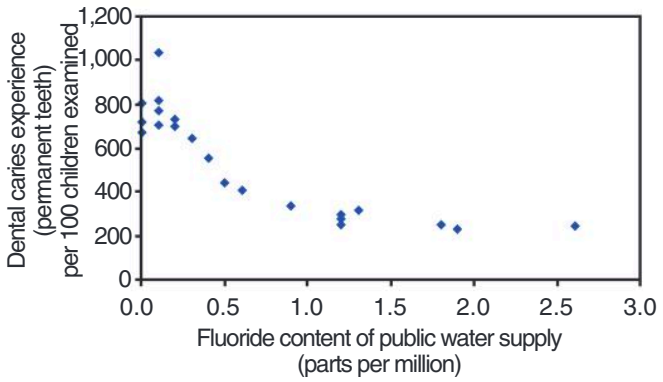


Fig. 1.7 Relationship between rate of dental caries in children's permanent teeth and fluoride content of public water supply. (Modified from Dean HT, Arnold Jr FA, Elvove E. Domestic water and dental caries: V. Additional studies of the relation of fluoride in domestic waters to dental caries experience in 4,425 white children aged 12 to 14 years of 13 cities in 4 states. *Public Health Rep.* 1942;57:1155–1179.)

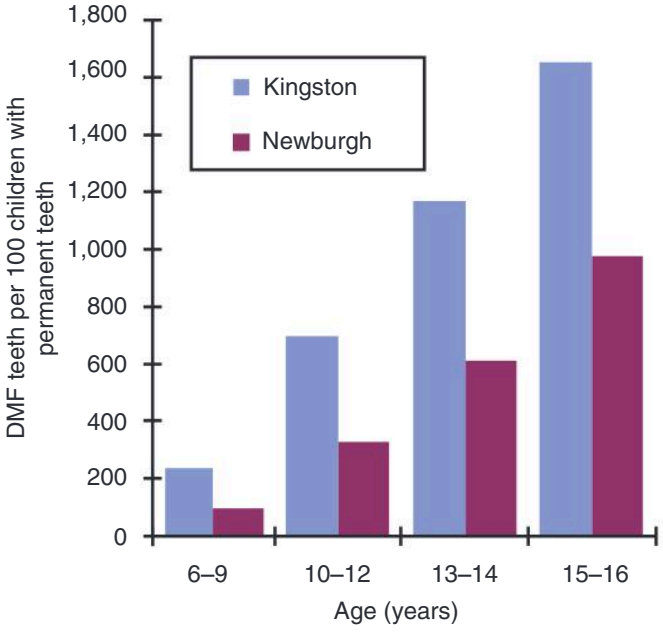


Fig. 1.8 Decayed, missing, and filled teeth *(DMF)* indices after 10 years of fluoridation, 1954–1955. (Modified from Ast DB, Schlesinger ER. The conclusion of a 10-year study of water fluoridation. *Am J Public Health.* 1956;46:265–271. Copyright 1956 by the American Public Health Association. Modified with permission.)

FROM OBSERVATIONS TO PREVENTIVE ACTIONS

In this section, three examples from history are discussed that demonstrate how epidemiologic observations have led to effective preventive measures in human populations.

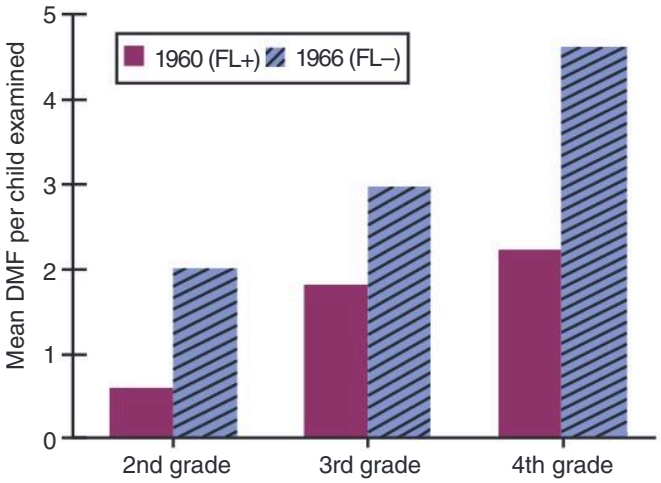


Fig. 1.9 Effect of discontinuing fluoridation in Antigo, Wisconsin, November 1960. *DMF,* Decayed, missing, and filled teeth; *FL+*, during fluoridation; *FL−*, after fluoridation was discontinued. (Modified from Lemke CW, Doherty JM, Arra MC. Controlled fluoridation: the dental effects of discontinuation in Antigo, Wisconsin. *J Am Dent Assoc.* 1970;80:782–786. Reprinted by permission of ADA Publishing Co., Inc.)

Ignáz Semmelweis and Childbed Fever

Ignáz Semmelweis (Fig. 1.10) was born in 1818 and began as a student of law until he left his studies to pursue medical training. He specialized in obstetrics and became interested in a major clinical and public health problem of the day: childbed fever, also known as puerperal fever (the word "puerperal" means related to childbirth or to the period after the birth).

In the early 19th century, childbed fever was a major cause of death among women shortly after childbirth, with mortality rates from childbed fever as high as 25%. Many theories of the cause of childbed fever were popular at the time, including atmospheric toxins, "epidemic constitutions" of some women, putrid air, or solar and magnetic influences. This period was a time of growing interest in pathologic anatomy. Because the cause of childbed fever remained a mystery, great interest arose in associating the findings at autopsies of women who had died of the disease with the clinical manifestations that characterized them while ill after childbirth.

Semmelweis was placed in charge of the First Obstetrical Clinic of the Allgemeine Krankenhaus (General Hospital) in Vienna in July 1846. At that time there were two obstetrical clinics, the First and the Second. Pregnant women were admitted for childbirth to the First

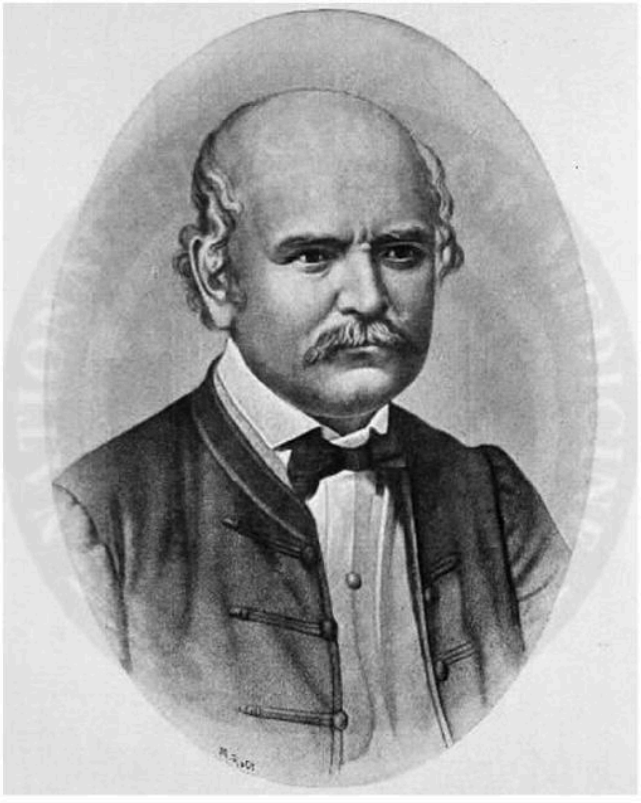


Fig. 1.10 Portrait of Ignáz Philipp Semmelweis. (From The National Library of Medicine.)

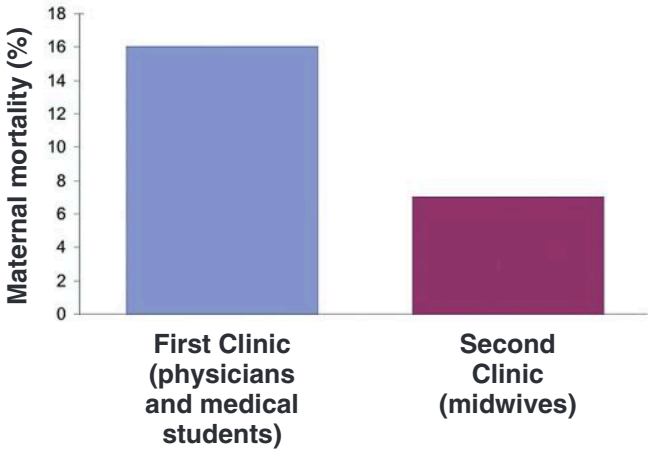


Fig. 1.11 Maternal mortality due to childbed fever, First and Second Clinics, General Hospital, Vienna, Austria, 1842. (Modified from the Centers for Disease Control and Prevention: Hand hygiene in health care settings—supplemental. www.cdc.gov/handhygiene/download/hand_hygiene_supplement.ppt. Accessed April 11, 2013.)

Clinic or to the Second Clinic on an alternating 24-hour basis. The First Clinic was staffed by physicians and medical students and the Second Clinic by midwives. Physicians and medical students began their days performing autopsies on women who had died from childbed fever; they then proceeded to provide clinical care for women hospitalized in the First Clinic for childbirth. The midwives staffing the Second Clinic did not perform autopsies. Semmelweis had been impressed by mortality rates in the two clinics in 1842 (Fig. 1.11). Mortality in the First Clinic was more than twice as high as in the Second Clinic—16% compared with 7%.

Semmelweis surmised that mortality was higher in the First Clinic than in the Second because the physicians and medical students went directly from the autopsies to their patients. Many of the women in labor had multiple examinations by physicians and by medical students learning obstetrics. Often these manual examinations traumatized the tissues of the vagina and uterus. Semmelweis suggested that the hands of physicians and medical students were transmitting disease-causing particles from the cadavers to the women who were about to deliver. His suspicions were confirmed in 1847 when his friend and colleague Jakob Kolletschka died from an infection contracted when he was accidentally punctured with a medical student's knife while performing an autopsy. The autopsy on Kolletschka showed pathology very similar to that of the women who were dying from childbed fever. Semmelweis concluded that physicians and medical students were carrying the infection from the autopsy room to the patients in the First Clinic and that this accounted for the high mortality rates from childbed fever in the First Clinic. Mortality rates in the Second Clinic remained low because the midwives who staffed the Second Clinic had no contact with the autopsy room.

Semmelweis then developed and implemented a policy for the physicians and medical students in the First Clinic, a policy designed to prevent childbed fever. He required the physicians and medical students in the First Clinic to wash their hands and to brush under their fingernails after they had finished the autopsies and before they encountered any of the patients. As seen in Fig. 1.12, in 1848, mortality in the First Clinic dropped from 12.2% to 2.4%, a rate comparable to that seen in the Second Clinic for the same year. When Semmelweis was later replaced by an obstetrician who did not subscribe to Semmelweis's theories, and who therefore eliminated the policy of required handwashing, mortality rates from childbed fever rose again in the First Clinic—further evidence supporting a causal relationship.

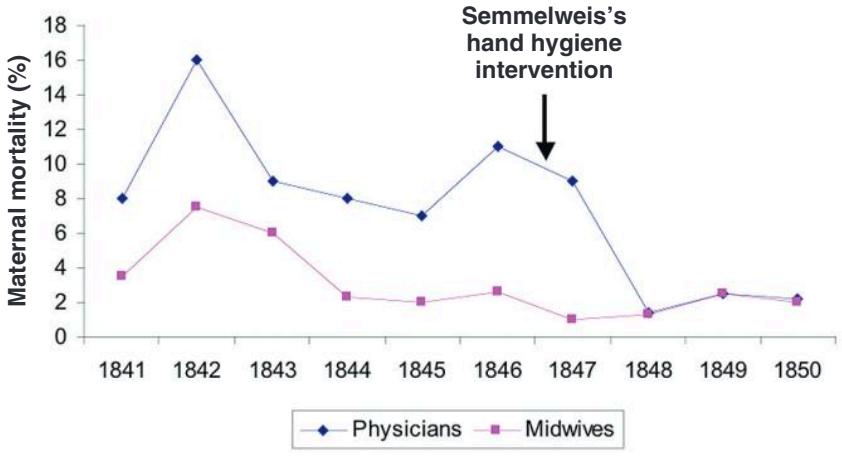


Fig. 1.12 Maternal mortality due to childbed fever, by type of care provider, General Hospital, Vienna, Austria, 1841–1850. (Modified from Mayhall GC. *Hospital Epidemiology and Infection Control*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 1999.)

Unfortunately, for many years Semmelweis refused to present his findings at major meetings or to submit written reports of his studies to medical journals. His failure to provide supporting scientific evidence was at least partially responsible for the failure of the medical community to accept his hypothesis of causation of childbed fever and his further proposed intervention of handwashing before examining each patient. Among other factors that fostered resistance to his proposal was the reluctance of physicians to accept the conclusion that by transmitting the agent responsible for childbed fever, they had been inadvertently responsible for the deaths of large numbers of women. In addition, physicians claimed that washing their hands before seeing each patient would be too time consuming. Another major factor is that Semmelweis was, to say the least, undiplomatic and had alienated many senior figures in medicine. Because of all of these factors, many years passed before a policy of handwashing was broadly adopted. An excellent biography of Semmelweis by Sherwin Nuland was published in 2003.[7]

The lessons of this story for successful policy making are still relevant today to the challenge of enhancing both public and professional acceptance of evidence-based prevention policies. These lessons include the need for clearly presenting supporting scientific evidence for a proposed intervention, the need for implementation of the proposed intervention to be perceived as feasible and cost-effective, and the need to lay the necessary groundwork for the policy, including garnering professional as well as community and political support.

Years later, the major cause of childbed fever was recognized to be a streptococcal infection. Semmelweis's major findings and recommendations ultimately had worldwide effects on the practice of medicine. Amazingly, his observations and suggested interventions preceded any knowledge of germ theory and thus proved that it is possible to implement a prevention strategy even when the exact cause of the disease is not known. However, it is also of interest that, although the need for handwashing has now been universally accepted, recent studies have reported that many physicians in hospitals in the United States and in other developed countries still fail to wash their hands as prescribed (Table 1.3).

TABLE 1.3 Compliance With Hand Hygiene Among Physicians, by Specialty, at University of Geneva Hospitals

Physician Specialty	No. of Physicians	Compliance With Hand Hygiene (% of Observations)
Internal medicine	32	87.3
Surgery	25	36.4
Intensive care unit	22	62.6
Pediatrics	21	82.6
Geriatrics	10	71.2
Anesthesiology	15	23.3
Emergency medicine	16	50.0
Other	22	57.2

Data from Pittet D. Hand hygiene among physicians: performance, beliefs, and perceptions. *Ann Intern Med.* 2004;141:1–8.

Fig. 1.13 Portrait of Edward Jenner. (From the Wellcome Historical Medical Museum and Library, London.)

Fig. 1.14 *Une des premières vaccinations d'Edward Jenner* ("One of the first vaccinations by Edward Jenner"), by Gaston Melingue. (Reproduced by permission of the Bibliothèque de l'Académie Nationale de Médecine, Paris, 2007.)

Edward Jenner and Smallpox

Edward Jenner (Fig. 1.13) was born in 1749 and became very interested in the problem of smallpox, which was a worldwide scourge. In the late 18th century, 400,000 people died from smallpox each year and one-third of survivors were blinded as a result of corneal infections. It was known that those who survived smallpox were subsequently immune to the disease, and consequently it became a common preventive practice to infect healthy individuals with smallpox by administering to them material taken from smallpox patients, a procedure called *variolation.* However, this was not the optimal method: some variolated individuals died from the resulting smallpox, infected others with smallpox, or developed other infections.

Jenner was interested in finding a better, safer approach to preventing smallpox. He observed, as had other people before him, that dairy maids, the young women whose occupation was milking cows, developed a mild disease called cowpox. Later, during smallpox outbreaks, smallpox appeared not to develop in these young women. In 1768 Jenner heard a claim from a dairy maid, "I can't take the smallpox for I have already had the cowpox." These data were observations and were not based on any rigorous study, but Jenner became convinced that cowpox could protect against smallpox and decided to test his hypothesis.

Fig. 1.14 shows a painting by Gaston Melingue of Edward Jenner performing the first vaccination in 1796. (The term "vaccination" is derived from *vacca*, the Latin word for "cow.") In this painting, a dairy maid, Sarah Nelmes, is bandaging her hand after just having had some cowpox material removed. The cowpox material is being administered by Jenner to an 8-year-old "volunteer," James Phipps. Jenner was so convinced that cowpox would be protective that 6 weeks later, to test his conviction, he inoculated the child with material that had just been taken from a smallpox pustule. The child did not contract the disease. We shall not deal in this chapter with the ethical issues and implications of this experiment. (Clearly, Jenner did not have to justify his study before an institutional review board!) In any event, the results of the first vaccination and of what followed eventually saved literally millions of human beings throughout the world from disability and death caused by the scourge of smallpox. The important point is that Jenner knew nothing about viruses and nothing about the biology of the disease. He operated purely on observational data that provided him with the basis for a preventive intervention.

In 1967 the World Health Organization (WHO) began international efforts to eradicate smallpox using

vaccinations with vaccinia virus (cowpox). It has been estimated that, until that time, smallpox afflicted 15 million people annually throughout the world, of whom 2 million died and millions of others were left blind or disfigured. In 1980 the WHO certified that smallpox had been eradicated. The smallpox eradication program,[8] directed at the time by Dr. D.A. Henderson (Fig. 1.15), is one of the greatest disease prevention achievements in human history. The WHO estimated that 350 million new cases had been prevented over a 20-year period. However, after the terrorist attacks that killed nearly 3,000 people in the World Trade Center in New York City on September 11, 2001, worldwide concern developed about potential bioterrorism in the wake of the 2001 anthrax attacks. Ironically, the possibility that smallpox virus might be used for such a purpose reopened issues regarding smallpox and vaccination that many thought had been permanently relegated to history by the successful efforts at eradication of the disease. The magnitude of the smallpox bioterrorism threat, together with issues of vaccinia risk—both to those vaccinated and to those coming in contact with vaccinees, especially in hospital environments—are among many that have had to be addressed. (It should, however, be noted that the cost-benefit of smallpox vaccination strongly favors benefit.[9]) However, often only limited or equivocal data are available on these issues to guide the development of relevant public health prevention policy relating to a potential bioterrorism threat of using smallpox as a weapon.

John Snow and Cholera

Another example of the translation of epidemiologic observations into public policy immortalized John Snow, whose portrait is seen in Fig. 1.16. Snow lived in the 19th century and was well known as the anesthesiologist who administered chloroform to Queen Victoria during childbirth. Snow's true love, however, was the epidemiology of cholera, a disease that was a major problem in England in the middle of the 19th century. In the first week of September 1854, approximately 600 people living within a few blocks of the Broad Street pump in London died of cholera. At that time, the Registrar General was William Farr. Snow and Farr

Fig. 1.15 Photograph of Dr. D.A. Henderson (1928–2016), who directed the World Health Organization Smallpox Eradication Program.

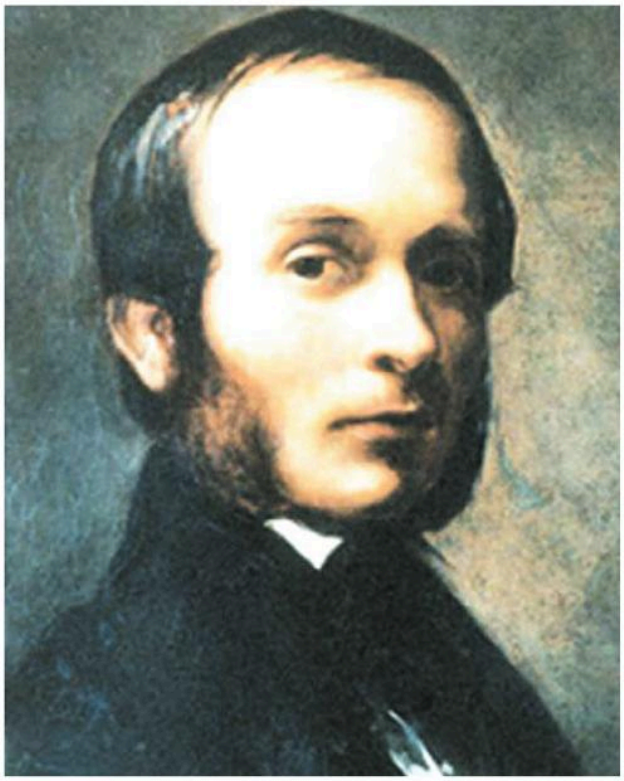


Fig. 1.16 Portrait of John Snow. (Portrait in oil by Thomas Jones Barker, 1847, in Zuck D. Snow, Empson and the Barkers of Bath. *Anaesthesia*. 2001;56:227–230.)

had a major disagreement about the cause of cholera. Farr adhered to what was called the *miasmatic* theory of disease. According to this theory, which was commonly held at the time, disease was transmitted by a *miasm*, or cloud, that clung low on the surface of the earth. If this were so, we would expect that people who lived at lower altitudes would be at greater risk of contracting a disease transmitted by this cloud than those living at higher elevations.

Farr collected data to support his hypothesis (Table 1.4). The data are quite consistent with his hypothesis: the lower the elevation, the higher the mortality rate from cholera. Snow did not agree; he believed that cholera was transmitted through contaminated water (Fig. 1.17). In London at that time, water was obtained by signing up with one of the water supply companies. The intakes for the water companies were in a very polluted part of the Thames River. At one point in time, one of the companies, the Lambeth Company, for technical, non–health-related reasons, shifted its water intake upstream in the Thames to a less polluted part of the river; the other companies did not move the locations of their water intakes. Snow reasoned therefore that based on his hypothesis that contaminated water caused cholera, the mortality rate from cholera would be lower in people getting their water from the Lambeth Company than in those obtaining their water from the other companies. He carried out what we

TABLE 1.4 Deaths From Cholera in 10,000 Inhabitants by Elevation of Residence Above Sea Level, London, 1848–1849

Elevation Above Sea Level (ft)	No. of Deaths
<20	102
20–40	65
40–60	34
60–80	27
80–100	22
100–120	17
340–360	8

Data from Farr W. *Vital Statistics: A Memorial Volume of Selections from the Reports and Writings of William Farr* (edited for the Sanitary Institute of Great Britain by Noel A. Humphreys). London: The Sanitary Institute; 1885.

Fig. 1.17 A drop of Thames water, as depicted by *Punch* in 1850. (From The wonders of a London water drop. *Punch Magazine*. May 11, 1850;461:188.)

currently call "shoe-leather epidemiology"—going from house to house, counting all deaths from cholera in each house, and determining which company supplied water to each house.

Snow's findings are shown in Table 1.5. The table shows the number of houses, the number of deaths from cholera, and the deaths per 10,000 houses. Although this is not an ideal way to calculate a rate, because a house can contain different numbers of people, it is not a bad approximation. We see that in houses served by the Southwark and Vauxhall Company, which obtained its water from a polluted part of the Thames, the death rate was 315 deaths per 10,000 houses. In homes supplied by the Lambeth Company, which had relocated its water intake upstream, the rate was only 38 deaths per 10,000 houses. His data were so convincing that they led Farr, the Registrar General, to require the registrar of each district in south London to record which water company supplied each house in which a person died of cholera. Remember that, in Snow's day, the enterotoxin *Vibrio cholerae* was unknown. Nothing was known about the biology of the disease. Snow's conclusion that contaminated water was associated with cholera was based entirely on observational data.[10]

The point is that, although it is extremely important for us to maximize our knowledge of the biology and pathogenesis of disease, it is not always necessary to know every detail of the possible pathogenic mechanisms to prevent disease. For example, we know that virtually every case of rheumatic fever and rheumatic heart disease occurred after a streptococcal infection. Though *Streptococcus* has been studied and analyzed extensively, we still do not know how and why it causes rheumatic fever. We do know that after a severe streptococcal infection, as seen in military recruits, rheumatic fever does not develop in 97 of every 100 infected persons. In civilian populations, such as schoolchildren, in whom the infection is less severe, rheumatic fever develops in only 3 of every 1,000 infected schoolchildren but not in the remaining 997.[11] Why does the disease not develop in those 97 recruits and 997 schoolchildren if they are exposed to the same organism? We do not know. Is the illness the result of an undetected difference in the organism, or is it caused by a cofactor that may facilitate the adherence of streptococci to epithelial cells? What we do know is that, even without fully understanding the chain of pathogenesis from infection with *Streptococcus* to rheumatic fever, we can prevent virtually every case of rheumatic fever if we either prevent or promptly and adequately treat streptococcal infections, as has been the case in the United States. The absence of biologic knowledge about pathogenesis should not be a hindrance or an excuse for not implementing effective preventive services.

Fig. 1.18 shows mortality data for breast cancer and lung cancer in women in the United States. Breast

TABLE 1.5 Deaths From Cholera per 10,000 Houses, by Source of Water Supply, London, 1854

Water Supply	No. of Houses	Deaths from Cholera	Deaths per 10,000 Houses
Southwark and Vauxhall Co.	40,046	1,263	315
Lambeth Co.	26,107	98	38
Other districts in London	256,423	1,422	56

Data modified from Snow J. On the mode of communication of cholera. In: *Snow on Cholera: A Reprint of Two Papers by John Snow, M.D.* New York: The Commonwealth Fund; 1936.

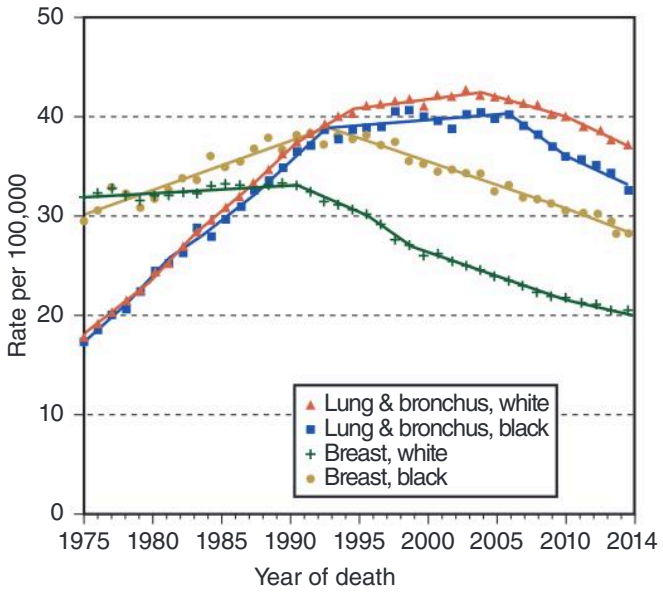


Fig. 1.18 Breast versus lung cancer mortality: White females versus Black females, United States, 1975–2014, age-adjusted to 2000 standard. (From Howlader N, Noone AM, Krapcho M, et al, eds. *SEER Cancer Statistics Review, 1975–2014, National Cancer Institute.* Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER website, April 2017. https://seer.cancer.gov/csr/1975_2014/browse_csr.php; *Figure 4.9.* Accessed April 14, 2017.)

cancer mortality rates remained relatively constant over several decades, but showed evidence of decline in the early years of the 21st century. However, mortality from lung cancer in women has been increasing steadily, although it may have begun to stabilize, and even decrease slightly, in recent years. Since 1987, more women in the United States have died each year from lung cancer than from breast cancer. We are therefore faced with the tragic picture of a largely preventable form of cancer, lung cancer, which results from a personal habit, smoking, as the current leading cause of cancer death in American women.

In 1993, environmental tobacco smoke (secondhand smoke from other people's smoking) was classified as a known human carcinogen by the Environmental Protection Agency, which attributed about 3,000 lung cancer deaths in nonsmoking individuals each year to environmental tobacco smoke.

WHEN THE FREQUENCY OF A DISEASE DECLINES, WHO DESERVES THE CREDIT?

Over the past hundred or so years, mortality rates from several common infectious diseases have declined in the United States. For example, deaths from childhood infections such as diphtheria, pertussis (whooping cough), and scarlet fever (a streptococcal infection) have declined dramatically. In addition, US deaths from tuberculosis have dropped significantly.

It would be tempting to link these declines to improvements in vaccines or treatments that became available for these diseases during this time. However, in 1971 Edward Kass published the graphs shown in Fig. 1.19.[12] These graphs demonstrate that for each of these diseases, the major decline in mortality occurred many years before any effective vaccine or treatment became available. Fig. 1.20 shows a similar presentation

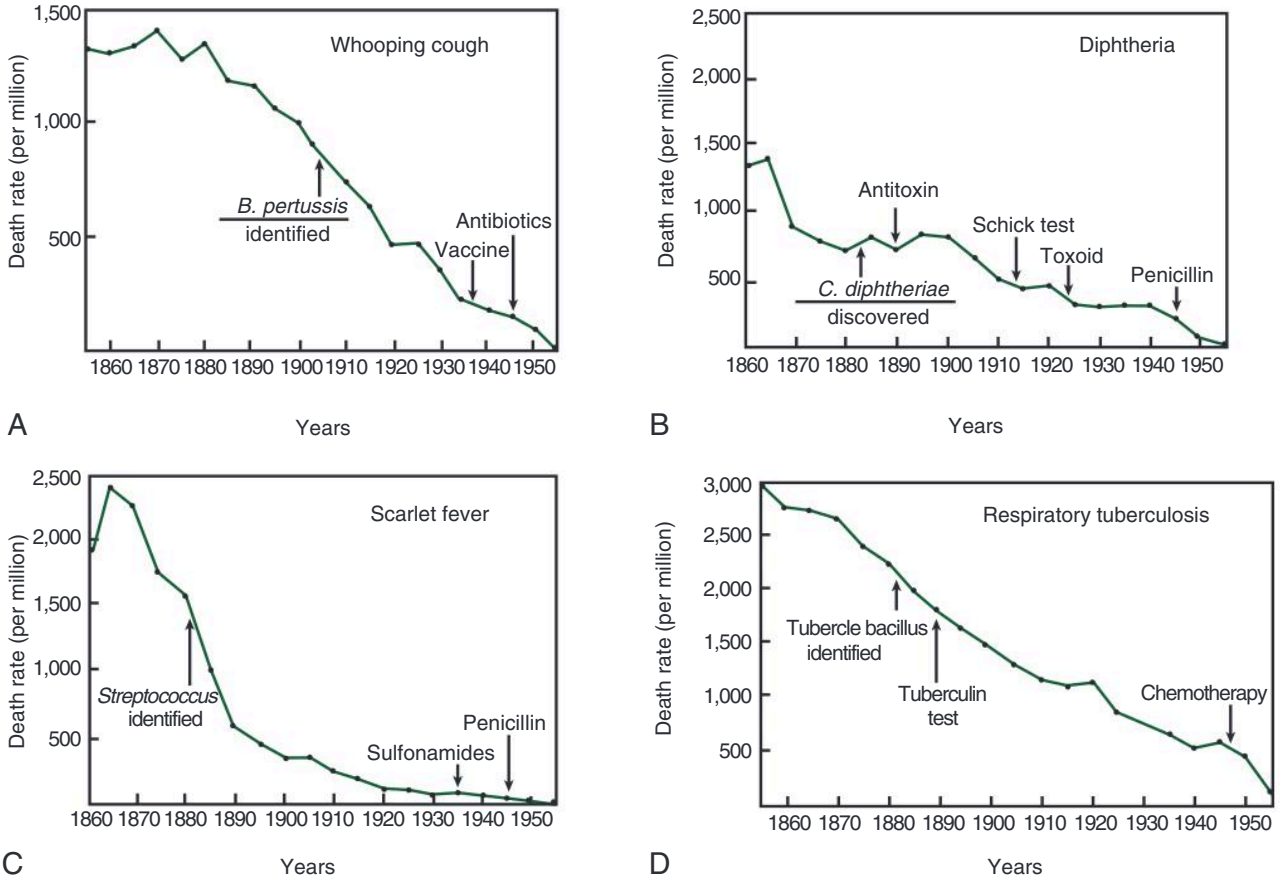


Fig. 1.19 Decline in death rates in England and Wales for **(A)** whooping cough, **(B)** diphtheria, **(C)** scarlet fever (children younger than 15 years of age), and **(D)** respiratory tuberculosis. (From Kass EH. Infectious diseases and social change. *J Infect Dis*. 1971;123:110–114.)

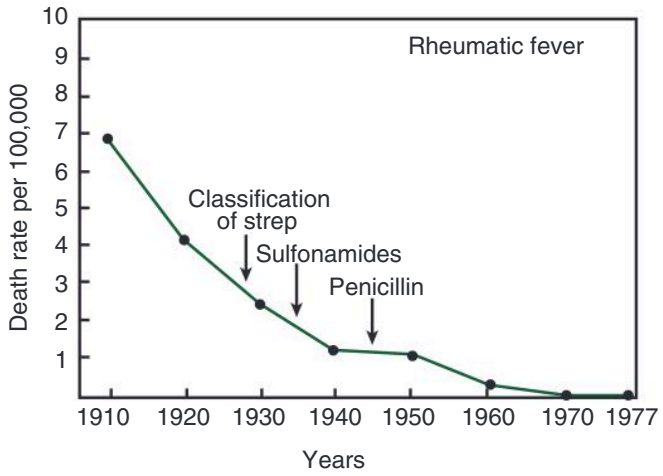


Fig. 1.20 Decline in crude death rates from rheumatic fever, United States, 1910–1977. (From Gordis L. The virtual disappearance of rheumatic fever in the United States: lessons in the rise and fall of disease. T. Duckett Jones Memorial Lecture. *Circulation*. 1985;72:1155–1162.)

of mortality trends over time for rheumatic fever in the 20th century.[13] Clearly, most of the decline in rheumatic fever mortality occurred well before penicillin and other antistreptococcal treatments became available.

What can explain these dramatic declines even before any vaccine or treatment became available? Theoretically, it is possible that when we observe a decline in mortality from an infectious disease, human exposure to the organisms involved may have declined, or the virulence of the organism may have diminished. However, a more likely explanation for the decline in mortality in these and other examples is that they primarily result from improvements in social conditions: safer water and reduced exposures to pollutants unrelated to any medical intervention. In fact, Kass titled his 1971 paper, in which the graphs in Fig. 1.19 appeared, "Infectious Diseases and Social Change." Although the specific factors that were probably involved are not always clear, social determinants of health, including improved housing, sanitation and nutrition, in addition to simultaneous lifestyle changes, are major factors that are likely to have contributed significantly to the decline.

We are often eager to attribute temporal declines in mortality to medical interventions. However, the lesson illustrated by the examples presented here is that we should be cautious before we conclude that observed declines in mortality are a result of medical intervention. In view of difficulties in deriving inferences about the effectiveness of medical care solely from population-wide declines in mortality, rigorous epidemiologic studies are clearly essential to assess the effectiveness of different medical interventions. Some of the approaches used and the design of such studies for evaluating health services are discussed in Chapter 17.

INTEGRATING PREVENTION AND TREATMENT

Prevention and therapy all too often are viewed as mutually exclusive activities, as is shown in Fig. 1.21. However, prevention is integral to public health, but it is also integral to clinical practice. The physician's role is to maintain health, as well as to treat disease, but even treatment of disease includes a major component of prevention, which often involves other health care workers. Whenever we treat illness, we are preventing death, preventing complications in the patient, or preventing the impact on the patient's family. Thus, much

Fig. 1.21 Prevention and therapy viewed as mutually exclusive activities. (ZIGGY © 1986 ZIGGY AND FRIENDS, INC. Reprinted with permission of ANDREWS MCMEEL SYNDICATION. All rights reserved.)

of the dichotomy between therapy and prevention is an illusion. Therapy involves secondary and tertiary prevention, the latter denoting the prevention of complications such as disability. At times it also involves primary prevention. Thus, the entire spectrum of prevention should be viewed as integral to both public health and clinical practice.

Two very different decisions in 2012 placed further emphasis on the link between prevention and treatment. In July 2012 the US Food and Drug Administration (FDA) approved the use of a drug, Truvada (combination tenofovir and emtricitabine [antiviral medications]; Gilead Sciences, Foster City, CA, United States), for preventing HIV infection in people who are at high risk of acquiring HIV infection (so-called preexposure prophylaxis [PrEP]). Since 2004 the drug had been marketed only for treatment of individuals already infected with HIV—both for those chronically infected and those exposed to a needle-stick or other traumatic risk (so-called postexposure prophylaxis [PEP]).

CONCLUSION

Epidemiology is an invaluable tool for providing a rational basis on which effective prevention programs can be planned and implemented. Epidemiology is valuable when conducting clinical investigations to evaluate both newly developed interventions for disease prevention as well as new therapies and those that have been in use for some time. The goal is to improve the control of disease through both prevention and treatment that will prevent deaths from the disease and will enhance the quality of life of those who have developed serious illness. The study designs used in epidemiology are discussed in later chapters.

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2

The Dynamics of Disease Transmission

I keep six honest serving-men
(They taught me all I knew);
Their names are What and Why and When
And How and Where and Who.
—Rudyard Kipling[1] (1865–1936)

LEARNING OBJECTIVES

- To introduce concepts related to disease transmission using the epidemiologic approach to communicable diseases as a model.
- To define important terms related to the occurrence of disease in a population.
- To calculate an attack rate and illustrate how it may be used to measure person-to-person transmission of a disease.
- To describe the steps in an outbreak investigation and introduce how cross-tabulation may be used to identify the source.

Human disease does not arise in a vacuum. It results from an interaction of the host (a person), the agent (e.g., a bacterium), and the environment (e.g., polluted air). Although some diseases are largely genetic in origin, virtually all disease results from an interaction of genetic, behavioral, and environmental factors, with the proportions differing for different diseases. Many of the underlying principles governing the transmission of disease are most clearly demonstrated using communicable diseases as a model. Hence this chapter primarily uses such diseases as examples in reviewing these principles. However, the concepts discussed are also applicable to diseases that are not infectious in origin (e.g., second-hand smoke causing cancer).

Disease has been classically described as the result of the epidemiologic triad shown in Fig. 2.1. According to this diagram, it is the product of an interaction of the human host, an infectious or other type of agent, and the environment that promotes the exposure. A vector, such as the mosquito or the deer tick, may be involved. For such an interaction to take place, the host must be susceptible. Human susceptibility is determined by a variety of factors including genetic background and behavioral, nutritional, and immunologic characteristics. The immune status of an individual is determined by many factors including prior experience both with natural infection and with immunization.

The factors that can cause human disease include biologic, physical, and chemical factors as well as other types, such as stress or behavioral risks, which may be harder to classify (Table 2.1).

MODES OF TRANSMISSION

Diseases can be transmitted *directly* or *indirectly*. For example, a disease can be transmitted from person to person (direct transmission) by means of direct contact (as in the case of sexually transmitted infections).

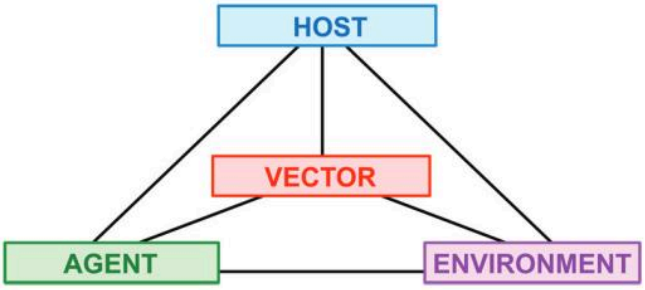


Fig. 2.1 The epidemiologic triad of a disease.

TABLE 2.1 Factors That May Be Associated With Increased Risk of Human Disease

Host Characteristics	Types of Agents and Examples	Environmental Factors
Age	Biologic	Temperature
Sex	Bacteria,	Humidity
Race	viruses	Altitude
Religion	Chemical	Crowding
Customs	Heavy metals,	Housing
Occupation	alcohol,	Neighborhood
Genetic profile	smoke	Water
Marital status	Physical	Milk
Family	Trauma,	Food
background	radiation, fire	Radiation
Previous	Nutritional	Air pollution
diseases	Lack, excess	Noise
Immune status		

BOX 2.1 Modes of Disease Transmission

1. Direct
   a. Person-to-person contact
2. Indirect
   a. Common vehicle
      1) Single exposure
      2) Multiple exposures
      3) Continuous exposure
   b. Vector

Indirect transmission can occur through a common vehicle such as a contaminated air or water supply or by a vector such as the mosquito. Some of the modes of transmission are shown in Box 2.1.

Fig. 2.2 is a classic photograph showing droplet dispersal after a sneeze. It vividly demonstrates the potential

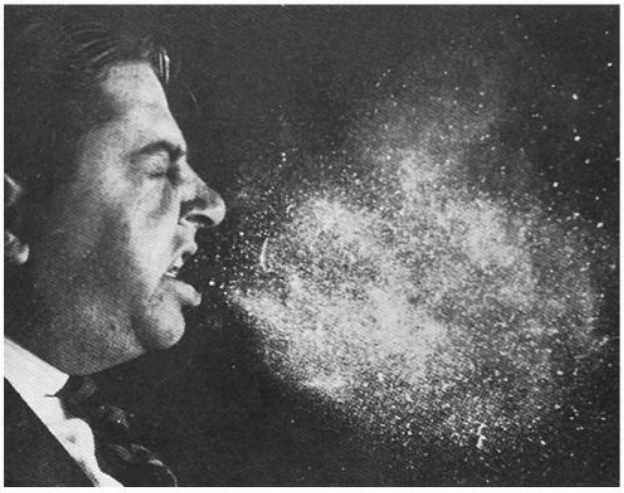


Fig. 2.2 Droplet dispersal following a violent sneeze. (Reprinted with permission from Jennison MW. *Aerobiology*. 17:102, 1947. Copyright 1947 American Association for the Advancement of Science.)

for an individual to infect many people in a brief period of time. As Mims has pointed out:

> *An infected individual can transmit influenza or the common cold to a score of others in the course of an innocent hour in a crowded room. A venereal infection also must spread progressively from person to person if it is to maintain itself in nature, but it would be a formidable task to transmit venereal infection on such a scale.*[2]

Thus, different organisms spread in different ways, and the potential of a given organism for spreading and producing outbreaks depends on the characteristics of the organism, such as its rate of growth, the route by which it is transmitted from one person to another, and the number of susceptible persons in the community.

Fig. 2.3 is a schematic diagram of human body surfaces as sites of microbial infection and shedding. The alimentary tract can be considered as an open tube that crosses the body, and the respiratory and urogenital systems are shown as blind pockets. Each offers an opportunity for infection. The skin is another important portal of entry for infectious agents, primarily through scratches, bites, or injury. Agents that often enter through the skin include streptococci or staphylococci and fungi such as tinea (ringworm). Two points should be made in this regard: first, the skin is not the

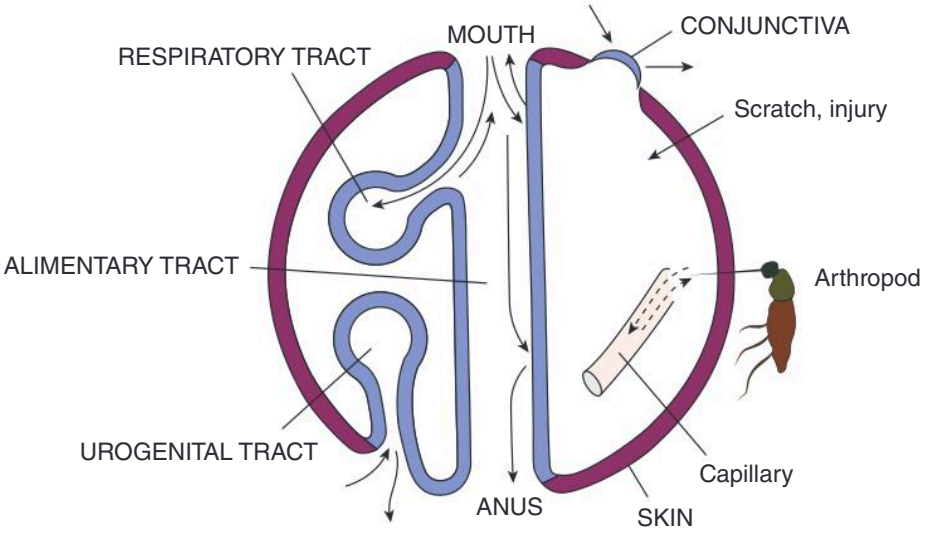


Fig. 2.3 Body surfaces as sites of microbial infection and shedding. (From Mims CA, Nash A, Stephen J. *Mims' Pathogenesis of Infectious Disease*. 5th ed. London: Academic Press; 2001.)

exclusive portal of entry for many of these agents, and second, infections can be acquired through more than one route. The same routes also serve as points of entry for noninfectious disease-causing agents. For example, environmental toxins can be ingested, inspired during respiration, or absorbed directly through the skin. The clinical and epidemiologic characteristics of many infectious and noninfectious conditions often relate to the site of the exposure to an organism or to an environmental substance and to its portal of entry into the body.

Another example of more than one mode of transmission is the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative virus of coronavirus disease 19 (COVID-19). While the primary mode of transmission of SARS-CoV-2 is through exposure to respiratory fluids carrying infectious virus by inhalation of air carrying infectious virus, deposition of virus carried in droplets onto exposed mucous membranes or touching infected mucous membranes with hands that were contaminated with droplet-containing infectious virus may occur.[3]

CLINICAL AND SUBCLINICAL DISEASE

It is important to recognize the broad spectrum of disease severity. Fig. 2.4 shows the iceberg concept of disease. Just as most of an iceberg is under water and hidden from view with only its tip visible, so it is with disease: only clinical illness is readily apparent (as seen

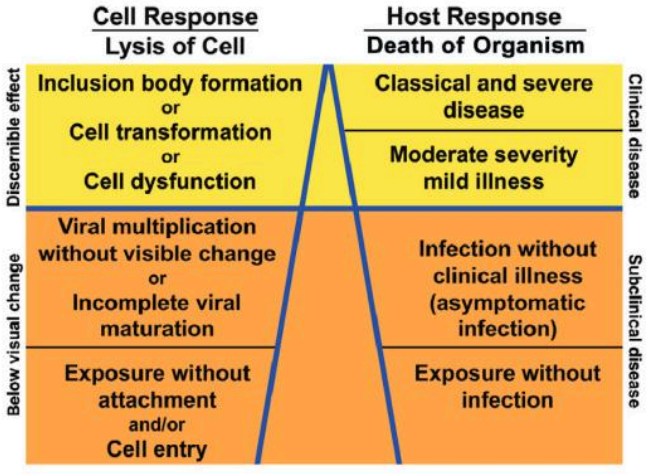


Fig. 2.4 The "iceberg" concept of infectious diseases at the level of the cell and of the host. (Modified from Evans AS, Kaslow RA, eds. *Viral Infections of Humans: Epidemiology and Control*. 4th ed. New York: Plenum; 1997.)

under *Host Response* on the *right* side of Fig. 2.4). However, infections without clinical illness are important, particularly in the web of disease transmission, although they are not clinically apparent. In Fig. 2.4, the corresponding biologic stages of pathogenesis (biologic mechanisms) and disease at the cellular level are seen on the *left*. The iceberg concept is important because it is not sufficient to count only the clinically apparent cases we see; for example, most cases of polio in prevaccine days were subclinical—that is, many people who contracted polio infection were not clinically ill.

Nevertheless, they were still capable of spreading the virus to others. So too is SARS CoV-2. As a result, we cannot understand and explain the spread of polio or COVID-19 unless the pool of inapparent cases (subclinical) is recognized and tested. From the viewpoint of inapparent disease, this situation is not any different in many noncommunicable diseases. Although these diseases are not spread from person to person, many individuals, for example, can live a long time with inapparent chronic kidney disease, and it is only when they experience a clinical complication that a diagnosis of chronic kidney disease is made.

Fig. 2.5 shows the spectrum of severity for several diseases. Most cases of tuberculosis, for example, are inapparent. However, because inapparent cases can transmit the disease, such cases must be identified and treated to control the further spread of the disease. In measles, many cases are of moderate severity and only a few are inapparent. At the other extreme, without intervention, rabies has no inapparent cases, and most untreated cases are fatal. Thus, we have a spectrum of severity patterns that vary with the disease. Severity appears to be related to the virulence of the organism (how efficient the organism is at producing disease) and to the site in the body where the organism multiplies. All these factors, as well as such host characteristics as the immune response, must be appreciated to understand how disease spreads from one individual to another.

As clinical and biologic knowledge has increased over the years, so has our ability to distinguish different stages of disease. These include clinical and nonclinical disease.

Clinical Disease

Clinical disease is characterized by signs and symptoms.

Nonclinical (Inapparent) Disease

Nonclinical disease may include the following:

1. *Preclinical disease:* Disease that is not yet clinically apparent but is destined to progress to clinical disease.
2. *Subclinical disease:* Disease that is not clinically apparent and is not destined to become clinically apparent. This type of disease is often diagnosed by serologic (antibody) response or culture of the organism.
3. *Persistent (chronic) disease:* A person fails to "shake off" the infection, and it persists for years, at times for life. In recent years, an interesting phenomenon has been the manifestation of symptoms many years after an infection was thought to have been resolved. Some adults who recovered from poliomyelitis in childhood report severe chronic fatigue and weakness; this has been called post-polio syndrome in adult life. These have thus become cases of clinical disease, albeit somewhat different from the initial illness. Long COVID is another example that we have recently identified.
4. *Latent disease:* An infection with no active multiplication of the agent, as when viral nucleic acid is incorporated into the nucleus of a cell as a provirus.

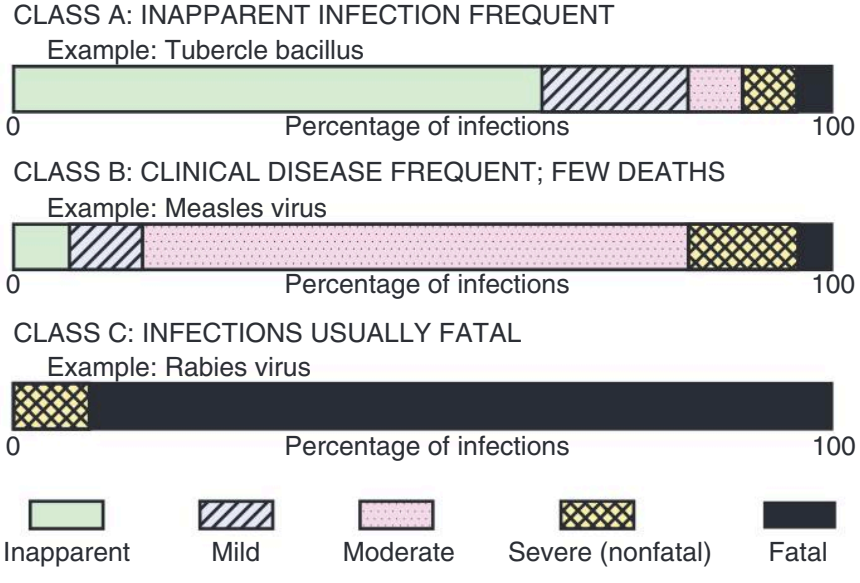


Fig. 2.5 Distribution of clinical severity for three classes of infections (not drawn to scale). (Modified from Mausner JS, Kramer S. *Epidemiology: An Introductory Text*. Philadelphia: WB Saunders; 1985:265.)

In contrast to persistent infection, only the genetic message is present in the host, not the viable organism.

CARRIER STATUS

A carrier is an individual who harbors the organism but is not infected as measured by serologic studies (no evidence of an antibody response) or shows no evidence of clinical illness. This person can still infect others, although the infectivity is generally lower than with other infections. Carrier status may be of limited duration or may be chronic, lasting for months or years. One of the best-known examples of a long-term carrier was Mary Mallon (1869–1938), better known as Typhoid Mary, who carried *Salmonella typhi* and died in 1938. Over a period of many years, she worked as a cook in the New York City area, moving from household to household under different names. She was considered to have caused at least 10 typhoid fever outbreaks that included 51 cases and 3 deaths.

Carrier status also refers to those individuals who have the causative organism without a clinical disease. These can be considered either *asymptomatic* or *presymptomatic*. A contemporary example for this carrier status is those individuals who are harboring SARS-CoV-2 but do not exhibit any symptoms, and subsequently are not tested to detect the virus in their respiratory fluids. Several reports have documented that these individuals can spread infection to others without even knowing that they are transmitting it, and some suggested that the majority of transmission occurs in the *asymptomatic* or *presymptomatic* statuses.[4,5] This becomes of critical importance to public health officials trying to issue guidelines for the public to limit the transmission of disease. Furthermore, it becomes difficult for these individuals with *carrier status* to take proper precautions as they interact with their usual contacts, e.g., isolation, wearing masks, social distancing, etc.

ENDEMIC, EPIDEMIC, AND PANDEMIC

Three other terms must be defined: *endemic, epidemic,* and *pandemic*. *Endemic* is defined as the habitual presence of a disease within a given geographic area. It may also refer to the usual occurrence of a given disease within such an area (sometimes referred to as the "background rate of disease"). *Epidemic* is defined as the occurrence in a community or region of a group of illnesses of similar nature, clearly in excess of normal expectancy and derived from a common or a propagated source (Fig. 2.6). *Pandemic* refers to a worldwide epidemic.

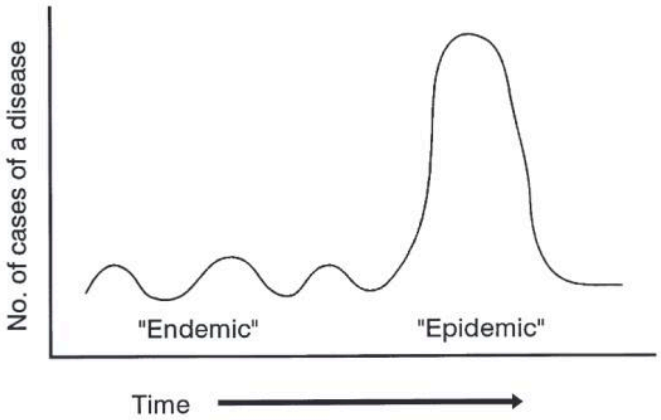


Fig. 2.6 Endemic versus epidemic disease.

How do we know when we have an excess over what is expected? Indeed, how do we know how much to expect? There is no precise answer to either question. Through ongoing surveillance, we may determine what the usual or expected level may be. With regard to excess, sometimes an "interocular test" may be convincing: the difference is so clear that it hits you between the eyes.

Two examples will show how pandemics and fear of pandemics relate to the development of public policy. The first and most recent example is the emergence of SARS-CoV-2, the causative virus of COVID-19 in late 2019. It was initially seen as a mysterious illness that led to pneumonia and death. Given the ease of global transportation, the spread of the infection was exponential. On January 30, 2020, the World Health Organization (WHO) identified COVID-19 as a Public Health Emergency of International Concern, which is the highest level of alarm by the WHO. On March 11, 2020, the WHO formally classified it as a pandemic, and by April 4, 2020, WHO reported that at least 1 million individuals had been identified as a confirmed case of COVID-19—a 10-fold increase in less than a month.[6] Governments across the world imposed travel restrictions, travel bans, shelter-in-place orders, business lockdowns,

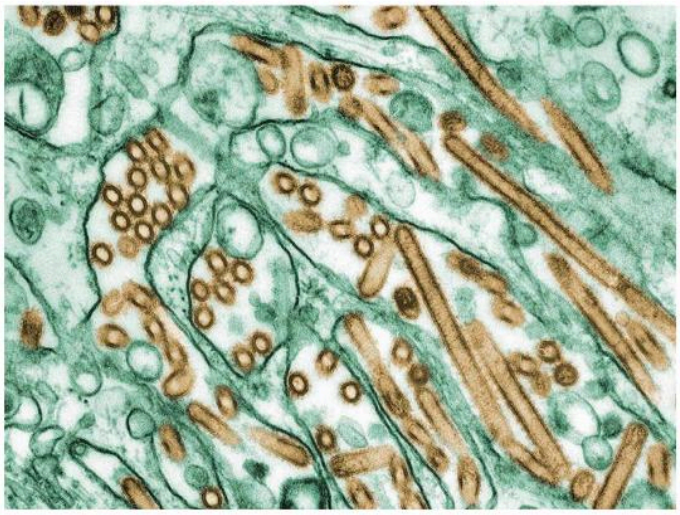


Fig. 2.7 Colorized transmission electron micrograph of avian influenza A H5N1 viruses (seen in *gold*) grown in MDCK cells (seen in *green*). (From Centers for Disease Control and Prevention, Courtesy Cynthia Goldsmith, Jacqueline Katz, and Sherif R. Zaki.)

and school closures to limit the transmission of the disease and reduce the strain on the already-overwhelmed healthcare systems. This was coupled with a worldwide shortage in the availability and even production of personal protective equipment. A recent example of an epidemic is the mpox outbreak in the US which primarily affected bisexual people and men who have sex with men. The mpox epidemic is dramatically reduced from the situation in 2021-2022, in large part because of the vaccinations.

The second example involves an issue that arose in 2011 related to laboratory research into the H5N1, or "bird flu," virus (Fig. 2.7). Although transmission of naturally occurring H5N1 has been primarily limited to persons having direct contact with infected animals, in the unusual cases where people do acquire the infection from animals, the disease is often very severe with a high mortality. There has therefore been serious concern that certain mutations in the virus might increase transmissibility of the virus to humans and could therefore result in a human pandemic. In order to understand fully the possibility of such a mutation and the potential for preventing it, two government-funded laboratories, one at Erasmus Medical Center in the Netherlands and a second at the University of Wisconsin-Madison in the United States, created genetically altered H5N1 strains that could be transmitted between mammals (ferrets) through the air.

After reviewing the two studies, the US National Science Advisory Board for Biosecurity, for the first time in its history, recommended against publishing the details of the methodologies used in these studies. The board cited potential misuse by "*those who would seek to do harm*" by participating in bioterrorist activity. Other scientists, however, including members of an expert panel assembled by the World Health Organization (WHO), disagreed, stating that the work was important to public health efforts to prevent a possible pandemic in humans. In January 2012, a moratorium on some types of H5N1 research was self-imposed by the researchers to allow time for discussion of these concerns by experts and by the public. The results of the two studies were subsequently published in May and June of 2012.[7–9]

The major unresolved issue is whether the potential benefits to society from the results of these types of studies outweigh the risks from the uncontrolled spread of mutated virus, resulting from either lapse in biosafety in the laboratory (accidental release of the virus) or bioterrorist activity (intentional release of the virus). Scientists and policy makers are obliged to develop methods for assessing the risks and benefits of conducting different types of experimental research. In addition, these events illustrate that censorship and academic freedom in science remain highly relevant issues today.

DISEASE OUTBREAKS

Let us assume that a food becomes contaminated with a microorganism. If an outbreak occurs in the group of people who have eaten the food, it is called a *common-vehicle exposure*, because all the cases that occurred were in persons exposed to the suspected contaminated food. The food may be served only once—for example, at a catered luncheon—resulting in a *single exposure* to the people who eat it, or the food may be served more than once, resulting in *multiple exposures* to people who eat it more than once. When a water supply is contaminated with sewage because of leaky pipes, the contamination can be either *periodic*, causing multiple exposures as a result of changing pressures in the water supply system, which may cause intermittent contamination, or *continuous*, in which case a constant leak leads to persistent

contamination. The epidemiologic picture that is manifested depends on whether the exposure is single, multiple, or continuous.

For purposes of this discussion, we will focus on the *single-exposure, common-vehicle outbreak* because the issues discussed are most clearly seen in this type of outbreak. What are the characteristics of such an outbreak? First, such outbreaks are generally explosive—that is, there is a sudden and rapid increase in the number of cases of the disease or condition in a population. (Interestingly, single-exposure common-vehicle epidemics of noncommunicable diseases, such as the epidemic of leukemia following the explosion of an atomic bomb in Hiroshima and Nagasaki, also seem to follow the same pattern.) Second, the cases are limited to people who share the common exposure. This is self-evident, because in the first wave of cases we would not expect the disease to develop in people who were not exposed unless there was another independent source of the disease in the community. Third, in a food-borne outbreak, cases rarely occur in persons who did not eat the food—that is, those who acquire the disease from a primary case who ate the food. The reason for the relative rarity of such secondary cases in this type of outbreak is not well understood.

In the United States, the leading cause of food-borne–related illness is contamination with norovirus (from the Norwalk virus family). Globally, norovirus results in a total of $4.2 billion in direct health care system costs and $60.3 billion in societal costs per year.[10]

Over recent decades, a growing number of outbreaks of acute gastroenteritis (AGE) have occurred aboard cruise ships. The Centers for Disease Control and Prevention (CDC) has reported that rates of AGE among passengers on cruise ships have decreased from 27.2 cases per 100,000 travel days in 2008 to 22.3 in 2014, while the rate among crew members was essentially unchanged.[11] This could potentially be attributed to the production of operational manuals or specific guidelines providing hygiene standards, increasing awareness among passengers and crew members, communicable disease surveillance programs, and preventive procedures in addition to regulatory enforcement and strict inspections through the CDC's Vessel Sanitation Program (VSP), which monitors outbreaks on cruise ships and works to prevent

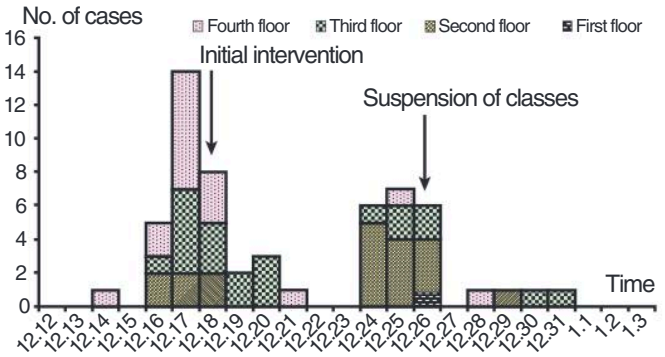


Fig. 2.8 Distribution of cases grouped by floor and by date of outbreak onset in a school in the province of in Jiangsu Province, China, in 2014. (From Shi C, Feng W-H, Shi P et al. An acute gastroenteritis outbreak caused by GII.17 norovirus in Jiangsu Province, China. *Int J Infect Dis.* 2016;49:30-32.)

and control transmission of illness aboard these ships. (Data from each outbreak are available on their website, http://www.cdc.gov/nceh/vsp/.) In areas with a high prevalence of norovirus, particularly the recombinant GII.2 type, such as in the provinces of Guangdong and Jiangsu, China, outbreaks of AGE continue to occur frequently.[12] For example, on December 14, 2014, a student in third grade vomited in the classroom and washroom several times and was considered the earliest suspected case of norovirus. Over the following 3 days, 27 more cases were reported, which were mainly located on the fourth floor (12 cases) and third floor (9 cases) of the school building. Fig. 2.8 shows the epidemic curve with the number of cases each day. The first peak of the outbreak was on December 17, which was starting to taper off when implementation of control measures such as quarantine and disinfection were followed. However, a few days later, on December 25, the attack rate peaked again, with cases occurring mainly on the second floor (12 cases) and third floor (5 cases). In order to aggressively contain the outbreak, the school was closed temporarily, and the outbreak came to an end on December 31.

IMMUNITY AND SUSCEPTIBILITY

The amount of disease in a population depends on a balance between the number of people in that population who are susceptible and therefore at risk for the disease and the number of people who are not susceptible or

immune and therefore not at risk. They may be immune because they have had the disease previously (and have antibodies) or because they have been immunized. They also may not be susceptible on a genetic basis. Clearly if the entire population is immune, no epidemic can develop. But the balance is usually struck somewhere in between immunity and susceptibility, and when it moves toward susceptibility, the likelihood of an outbreak increases. This has been observed particularly in formerly isolated populations who were later exposed to disease. For example, in the 19th century, Panum observed that measles occurred in the Faroe Islands in epidemic form when infected individuals entered the isolated and susceptible population.[13] In another example, severe outbreaks of streptococcal sore throats developed when new susceptible recruits arrived at the Great Lakes Naval Station.[14]

HERD IMMUNITY

Herd immunity is defined as the resistance of a group of people to an attack by a disease to which a large proportion of the members of the group are immune. If a large percentage of the population is immune, the entire population is likely to be protected, not just those who are immune. Why does herd immunity occur? It happens because disease spreads from one person to another in any community. Once a certain proportion of people in the community are immune, the likelihood is small that an infected person will encounter a susceptible person to whom he can transmit the infection; more of his encounters will be with people who are immune. The presence of a large proportion of immune persons in the population lessens the likelihood that a person with the disease will encounter a susceptible individual.

Why is the concept of herd immunity so important? When we carry out immunization programs, it may not be necessary to achieve 100% immunization rates to immunize the population successfully. We can achieve highly effective protection by immunizing a large part of the population; the remaining part will be protected because of herd immunity.

For herd immunity to exist, certain conditions must be met. The disease agent must be restricted to a single host species within which transmission occurs, and that transmission must be relatively direct from one member of the host species to another. If we have a reservoir in which the organism can exist outside the human host, herd immunity will not operate because other means of transmission may be available. In addition, infections must induce solid immunity. If immunity is only partial, we will not build up a large proportion of immune people in the community.

What does this mean? Herd immunity operates if the probability of an infected person encountering every *other individual* in the population ("random mixing") is the same. But if a person is infected and all his or her interactions are with people who are susceptible (i.e., there is no random mixing of the population), he or she is likely to transmit the disease to other susceptible people. Herd immunity operates optimally when populations are constantly mixing. This is a theoretical concept because, obviously, populations are never completely randomly mixed. All of us associate with family and friends, for example, more than we do with strangers. However, the degree to which herd immunity is achieved depends on the extent to which the population approaches a random mixing. Thus, we can interrupt the transmission of disease even if not everyone in the population is immune if a critical percentage of the population is immune.

What percentage of a population must be immune for herd immunity to operate? This percentage varies from disease to disease. For example, in the case of measles, which is highly communicable, it has been estimated that 94% of the population must be immune before the chain of transmission is interrupted. With decreasing childhood immunization rates in the United States associated with parental concerns regarding the risk of autism spectrum disorder, measles outbreaks are becoming more common. A total of 125 measles cases with rash occurred in a 6-week period; among these cases 110 were California residents (45% unvaccinated), of whom 35% had visited one or both Disney theme parks between December 17 and 20, 2014, the suspected source of exposure. Of the secondary cases, most (26/34) were close contacts. An additional 15 cases associated with the Disney theme parks were reported in seven additional states.[15]

Let us now consider poliomyelitis immunization and herd immunity. From 1951 to 1954, an average of 24,220 cases of paralytic poliomyelitis occurred in the United States each year. Two types of vaccine are available. The oral polio vaccine (OPV) protects not only

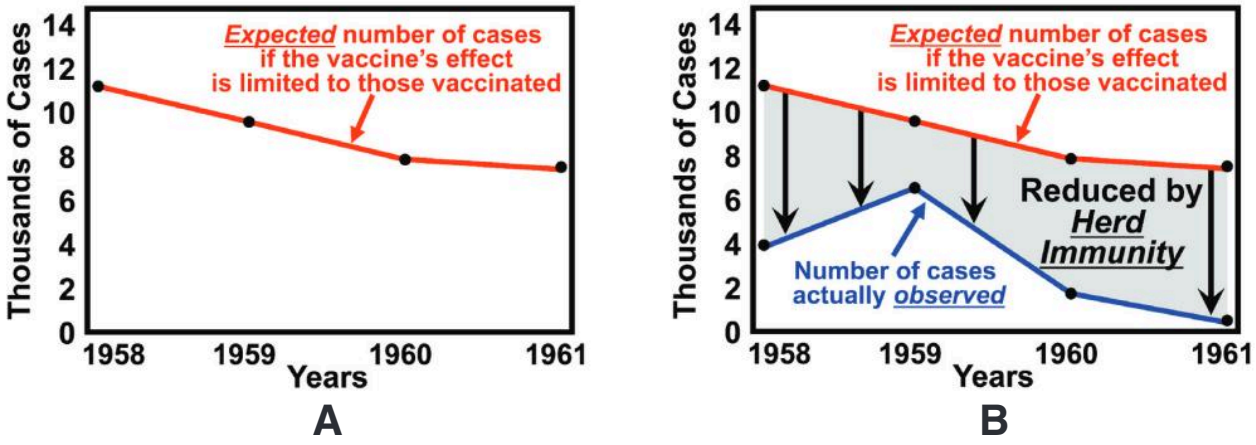


Fig. 2.9 Effect of herd immunity, United States, 1958–61. **(A)** Expected number of paralytic poliomyelitis cases if the vaccine's effect was limited to vaccinated people. **(B)** Number of cases observed as a result of herd immunity. (Modified from American Academy of Pediatrics News. Copyright 1998. From Stickle G. Observed and expected poliomyelitis in the United States, 1958–1961. *Am J Public Health*. 1964;54:1222-1229.)

those who are vaccinated but also others in the community through secondary immunity, produced when the vaccinated individual spreads the active vaccine virus to contacts. In effect, the contacts are immunized by the spread of virus from the vaccinated person. If enough people in the community are protected in this way, the chain of transmission is interrupted. However, even inactivated poliovirus vaccine (IPV), which does not produce secondary immunity (does not spread the virus to susceptible contacts), can produce herd immunity if enough of the population is immunized. Even those who are not immunized will be protected because the chain of transmission in the community has been interrupted.

From 1958 to 1961, only IPV was available in the United States. Fig. 2.9A shows the expected number of cases each year if the vaccine had protected only those who received the vaccine. Fig. 2.9B shows the number of polio cases observed. Clearly far fewer cases occurred than would have been expected from the direct effects of the vaccine alone. The difference between the two curves represents the effect of herd immunity from the vaccine. Thus, nonimmunized individuals can gain some protection from either the OPV or IPV.

INCUBATION PERIOD

The incubation period is defined as the *interval from receipt of infection to the time of onset of clinical illness* (the onset of recognizable symptoms). If you become infected today, the disease with which you are infected may not develop for several days or weeks. During this time, the *incubation period*, you feel completely well and show no signs of the disease.

Why does disease not develop immediately at the time of infection? What accounts for the incubation period? It may reflect the time needed for the organism to replicate sufficiently until it reaches the critical mass needed for clinical disease to result. It probably also relates to the site in the body at which the organism replicates—whether it replicates superficially, near the skin surface, or deeper in the body (e.g., in the gut). The dose of the infectious agent received at the time of infection may also influence the length of the incubation period. With a large dose, the incubation period may be shorter.

In the case of the COVID-19 pandemic, the incubation period was estimated to be 6.5 days from exposure to symptom onset.[16] However, it was shown that the mean incubation period during the Delta and Omicron variants have shorter incubation periods of 3–4 days.[17–19] The knowledge of the incubation period has significant clinical implication on the diagnosis, management, and public health response to exposure to positive cases with COVID-19.

The incubation period is also of historical interest because it is related to what may have been the only medical advance associated with the Black Death (plague) in Europe. In 1374, when people were terribly

frightened of the Black Death, the Venetian Republic appointed three officials who were responsible for inspecting all ships entering the port and for excluding ships that had sick people on board. It was hoped that this intervention would protect the community. In 1377, in the Italian seaport of Ragusa, travelers were detained in an isolated area for 30 days *(trentini giorni)* after arrival to see whether infection developed. This period was found to be insufficient, and the period of detention was lengthened to 40 days *(quarante giorni)*. This is the origin of the word *quarantine*.

How long would we want to isolate a person? We would want to isolate a person until he or she is no longer infectious to others (having passed through the suspected incubation period). When a person is clinically ill, we generally have a clear sign of potential infectiousness. An important problem arises *before* the person becomes clinically ill—that is, during the incubation period. If we knew when he or she became infected and knew the general length of the incubation period for the disease, we would want to isolate the infected person during this period (and perhaps a few days extra to be especially cautious) to prevent transmission of the disease to others. In most situations, however, we do not know that a person has been infected, and we may not know until signs of clinical disease become manifest. In addition, we may not know the distribution of the incubation period.

This leads to an important question: is it worthwhile to isolate a patient, such as a child with chickenpox? The problem is that, during at least part of the incubation period, when the person is still free of clinical illness, he or she can transmit the disease to others. Thus, we have people who are not (yet) clinically ill but who have been infected; they are unaware of their infection status and are able to transmit their disease. For many common childhood diseases, by the time clinical disease develops in the child, he or she has already transmitted the disease to others. Therefore, isolating such a person at the point at which he or she becomes clinically ill will not necessarily be effective. On the other hand, isolation can be very valuable. In September 2012, health officials in Saudi Arabia first reported a severe acute respiratory illness with symptoms of fever, cough, and shortness of breath. The causative organism was shown to be the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), which has an incubation period of about 5 or 6 days. MERS-CoV likely came from infected camels in the Arabian Peninsula and spread through person-to-person close contact, with health care personnel at higher risk of infection if universal precautions were not adhered to. All MERS-CoV cases that have been identified had a positive history of someone living in or traveling to countries in or near the Arabian Peninsula. Another outbreak of MERS-CoV occurred in the Republic of Korea in 2015 and was also linked to a returning traveler from the Arabian Peninsula. As of May 2017, WHO has reported that there had been 1952 laboratory-confirmed cases of infection with MERS-CoV from 27 countries, of whom 693 (36%) had died.

Fig. 2.10 shows the epidemic curve of weekly trends in number of COVID-19 cases in the US reported to the CDC from early 2020 to late 2022. (Note that, unlike the epidemic curve for common vehicle epidemics, the curve for person-to-person spread is multimodal.) While the first outbreak occurred in Wuhan, China, most probably in December 2019, every country around the world reported cases of COVID-19 within a few weeks.

Different diseases have different incubation periods. A precise incubation period does not exist for a given disease; rather, a range of incubation periods is characteristic of that disease. Fig. 2.11 shows the range of incubation periods for several diseases. In general, the length of the incubation period is a characteristic of the infective organism.

The incubation period for infectious diseases has its analogue in noninfectious diseases. Thus, even when an individual is exposed to a carcinogen or other environmental toxin, the disease is often manifest only after months or even years. For example, mesothelioma resulting from asbestos exposure may occur 20 to 30 years after the exposure. The incubation period for noninfectious diseases is often referred to as the *latency period.*

Fig. 2.12 is a graphic representation of an outbreak of *Salmonella typhimurium* at a medical conference in Wales in 1986. Each bar represents the number of cases of disease developing at a certain point in time after the exposure; the number of hours since exposure is shown along the horizontal axis. If we draw a line connecting the tops of the bars, it is called the *epidemic curve*, which is defined as the distribution of the times of onset of the disease. In a *single-exposure, common-vehicle epidemic,* the epidemic curve represents the distribution of the

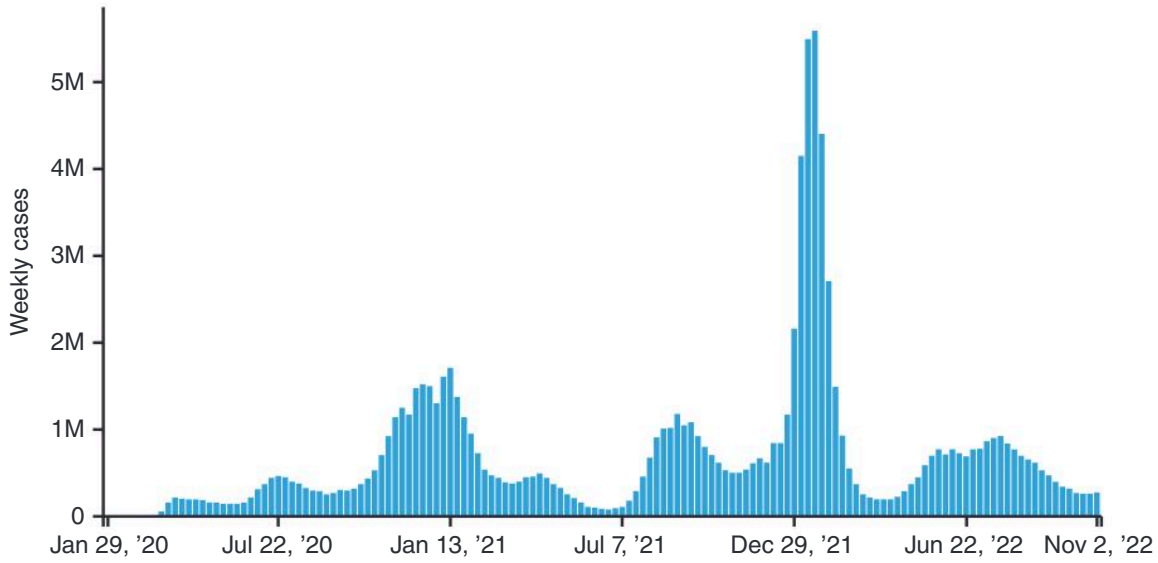


Fig. 2.10 Weekly trends in number of Covid-19 cases in the United States reported to the CDC. (From Centers for Disease Control and Prevention. COVID Data Tracker. Atlanta, GA: US Department of Health and Human Services, CDC; 2022, November 7. https://covid.cdc.gov/covid-data-tracker.)

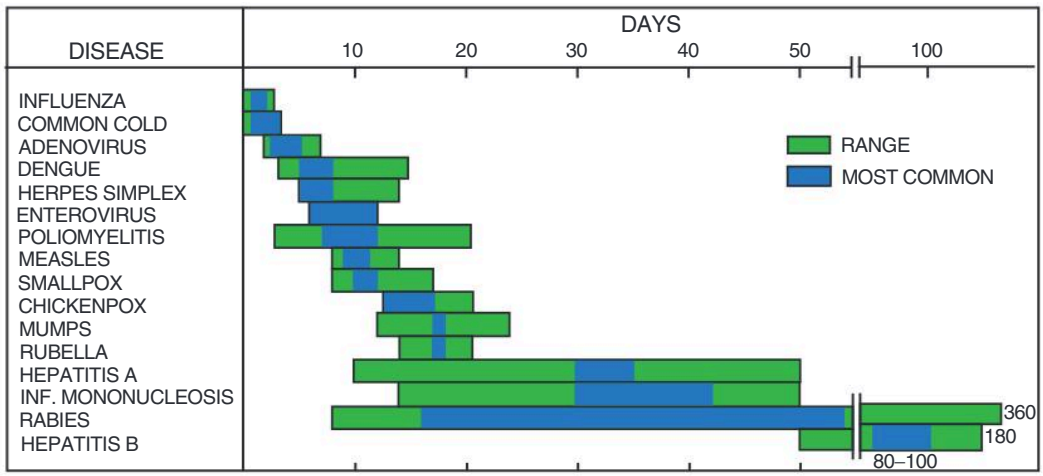


Fig. 2.11 Incubation periods of viral diseases. *INF.,* Infectious. (From Evans AS, Kaslow RA, eds. *Viral Infections of Humans: Epidemiology and Control*. 4th ed. New York: Plenum; 1997.)

incubation periods. This should be intuitively apparent: if the infection took place at one point in time, the interval from that point to the onset of each case is the incubation period in that person.

As seen in Fig. 2.12, involving *Salmonella typhimurium*, there was a rapid, explosive rise in the number of cases within the first 16 hours, which suggests a single-exposure, common-vehicle epidemic. In fact, this pattern is the classic epidemic curve for a single-exposure common-vehicle outbreak (Fig. 2.13, *left*). The reason for this configuration is not known, but it has an interesting property: if the curve is plotted against the logarithm of time rather than against time itself, the curve becomes a normal curve, which has useful statistical properties (see Fig. 2.13, *right*). If plotted on log-normal graph paper, we obtain a straight line, and estimation of the median incubation period is facilitated. Armenian and Lilienfeld[20] showed that a log-normal curve is also typical of single-exposure common-vehicle epidemics of noninfectious diseases.

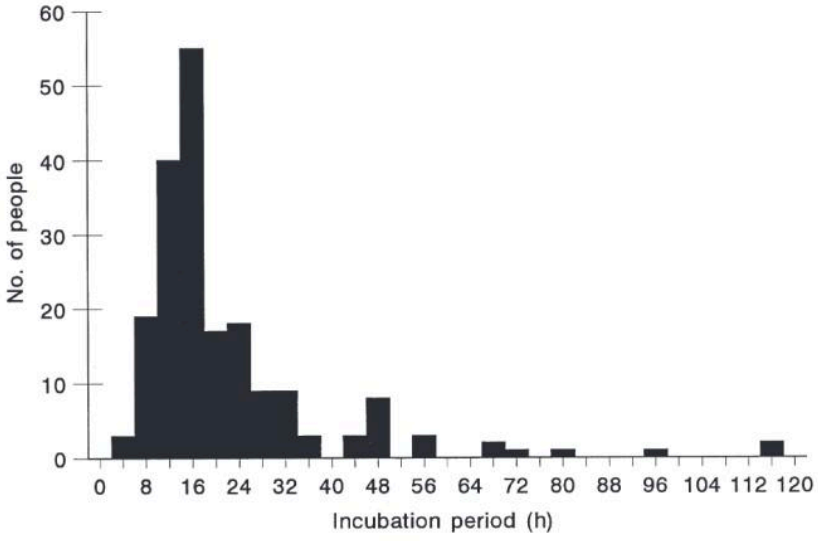


Fig. 2.12 Incubation periods for 191 delegates affected by a *Salmonella typhimurium* outbreak at a medical conference in Wales, 1986. (Modified from Glynn JR, Palmer SR. Incubation period, severity of disease, and infecting dose: evidence from a *Salmonella* outbreak. *Am J Epidemiol*. 1992;136:1369-1377.)

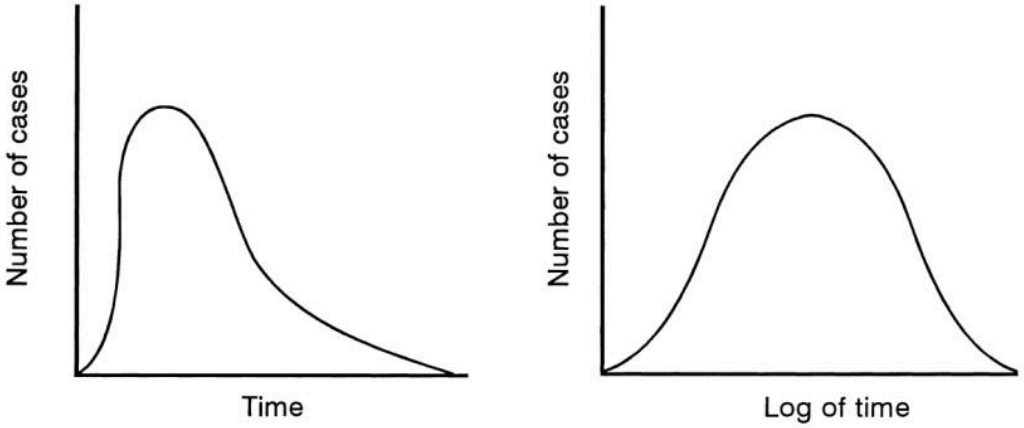


Fig. 2.13 Number of cases plotted against time and against the logarithm of time.

The three critical variables in investigating an outbreak or epidemic are as follows:

1. When did the exposure take place?
2. When did the disease begin?
3. What was the incubation period for the disease?

If we know any two of these, we can calculate the third.

ATTACK RATE

An attack rate is defined as:

$$\frac{\text{Number of people at risk in whom a certain illness develops}}{\text{Total number of people at risk}}$$

The attack rate is useful for comparing the risk of disease in groups with different exposures. The attack rate can be specific for a given exposure. For example, the attack rate in people who ate a certain food is called a *food-specific attack rate*. It is calculated by:

$$\frac{\text{Number of people who ate a certain food and became ill}}{\text{Total number of people who ate that food}}$$

In general, *time* is not explicitly specified in an attack rate because the exposure is common and the illness is acute—given what is usually known about how long after an exposure most cases develop, the time period is implicit in the attack rate.

A person who acquires the disease from that exposure (e.g., from a contaminated food) is called a *primary case*. A person who acquires the disease from exposure to a primary case is called a *secondary case*. The *secondary attack rate* is therefore defined as the attack rate in susceptible people who were not exposed to the suspected agent who have been exposed to a primary case. It is a good measure of person-to-person spread of disease after the disease has been introduced into a population, and it can be thought of as a ripple moving out from the primary case. We often calculate the secondary attack rate in family members of the index case.

The secondary attack rate also has application in non-infectious diseases when family members are examined to determine the extent to which a disease clusters among first-degree relatives of an index case (heritability or clustering within families), which may yield a clue regarding the relative contributions of genetic and environmental factors to the cause of a disease (think of secondary tobacco exposure and lung cancer in non-smokers).

EXPLORING OCCURRENCE OF DISEASE

The concepts outlined in this chapter form the basis for exploring the occurrence of disease. When a disease appears to have occurred at more than an endemic (usual) level and we wish to investigate its occurrence, we ask:

Who was attacked by the disease?

When did the disease occur?

Where did the cases arise?

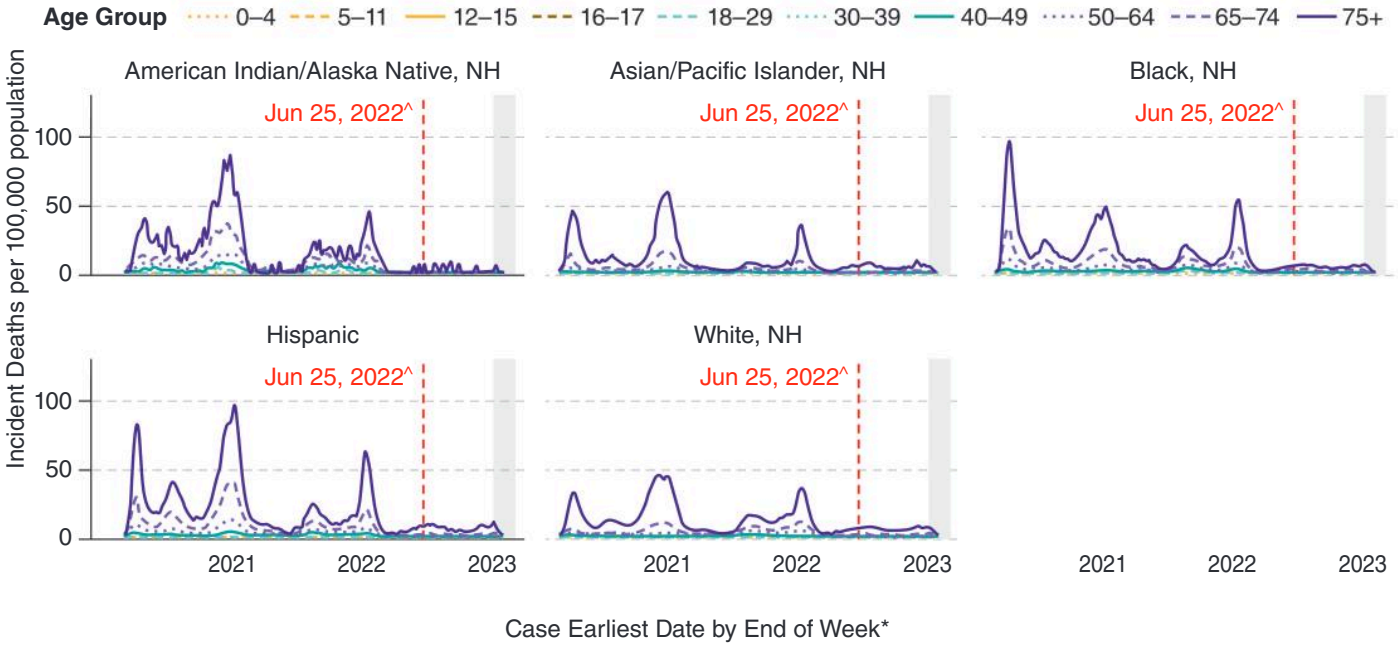
It is well known that disease risk is affected by all these factors.

Who?

The characteristics of the human host are clearly related to disease risk. Factors such as sex, age, and race/ethnicity as well as behavioral risk factors (e.g., smoking) may have major effects.

COVID-19

Fig. 2.14 shows the COVID-19 weekly deaths per 100,000 population by age and race/ethnicity in the US



US: Includes data up to the week ending on Feb 04, 2023. Percentage of deaths among reported cases - 0.97%. Percentage of deaths reporting race and age by date - 83.71%.
US territories are included in case and death counts but not in population counts. Potential six-week delay in case reporting to CDC denoted by gray bars. Weekly data with five or fewer deaths have been suppressed. *Case Earliest Date is the earliest of the clinical date (related to illness or specimen collection and chosen by a defined hierarchy) and the Date Received by CDC. The date for the current week extends through Saturday. ^The death rate for Texas during the week ending Jun 25, 2022, are reflective of a data reporting artifact.
Source: CDC COVID-19 Case Line-Level Data, 2019 US Census, HHS Protect; Visualization: Data, Analytics & Visualization Task Force and CDC CPR DEO Situational Awareness Public Health Science Team

Fig 2.14 COVID-19 weekly deaths per 100,000 population by age group and race/ethnicity, United States, March 01,2020–February 04, 2023.* (From Centers for Disease Control and Prevention. Covid Data Tracker. Atlanta, GA: US Department of Health and Human Services, CDC; 2023, February 4. https://covid.cdc.gov/covid-data-tracker).

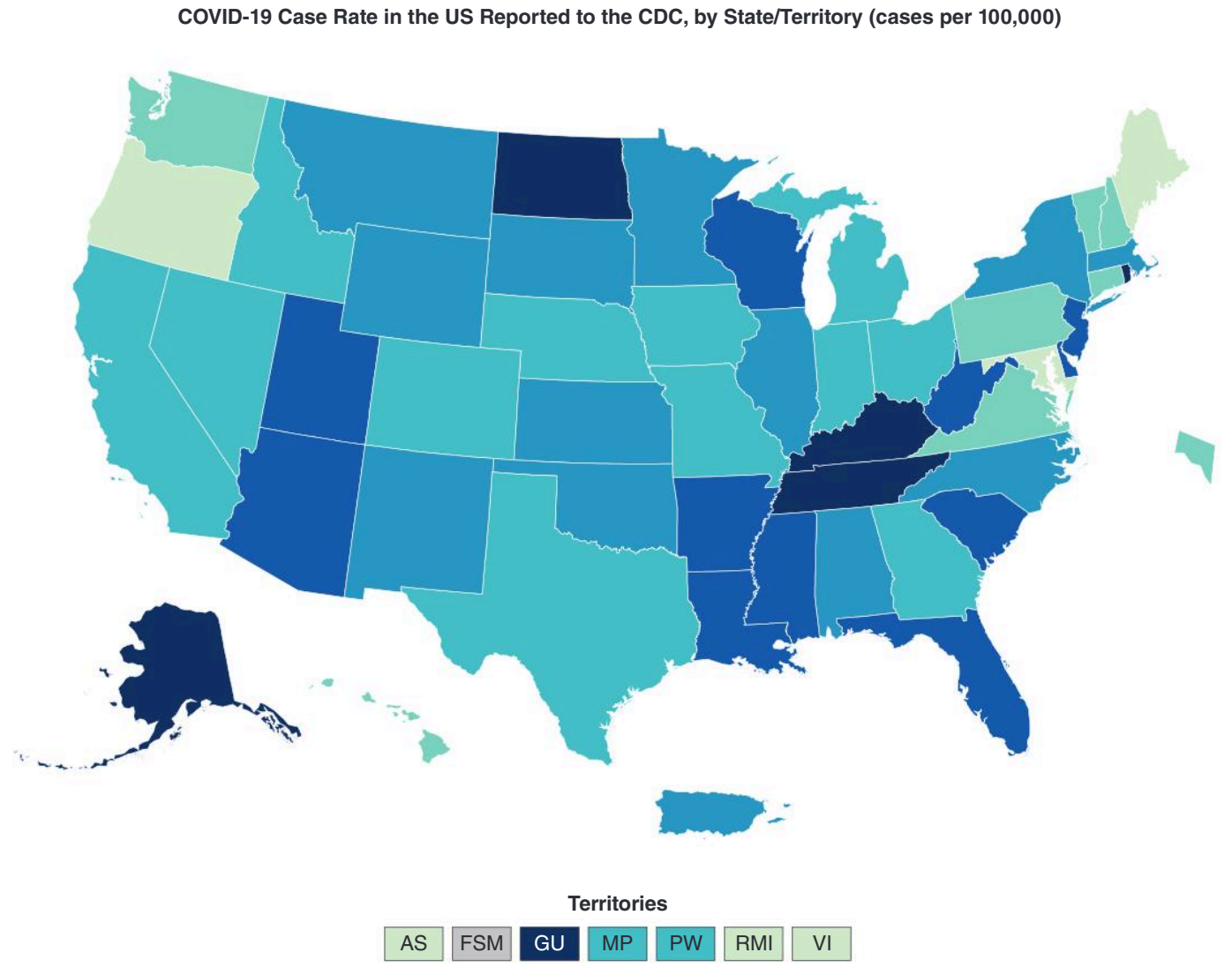


Fig 2.15 COVID-19 case rate in the US reported to the CDC, by state/territory (cases per 100,000). (From Centers for Disease Control and Prevention. COVID Data Tracker. Atlanta, GA: US Department of Health and Human Services, CDC; 2022, November 07. https://covid.cdc.gov/covid-data-tracker.)

from March 2020 to October 2022.[21] There is a clear disparity in the incident deaths per 100,000 population for the highest age group (75+ years), followed by those aged 65–74 years, compared with younger age groups. This is particularly evident in the first wave of the pandemic, and every wave of COVID-19 thereafter. On the other hand, there was geographical distribution of the COVID-19 cases throughout the US from the beginning of the pandemic. Fig. 2.15 shows COVID-19 case rates in the US reported to the CDC, by state/territory (cases per 100,000).[21] Alaska, Kentucky, North Dakota, Tennessee, and West Virginia had the highest case rates in the US, while Maine, Maryland, Oregon, Vermont, and Washington had the lowest case rates.

Gonorrhea

As shown in Fig. 2.16, rates of gonorrhea have historically been higher in males than in females, and this sex difference is observed at least as far back as 1960 (not shown in this graph). Because women are more likely

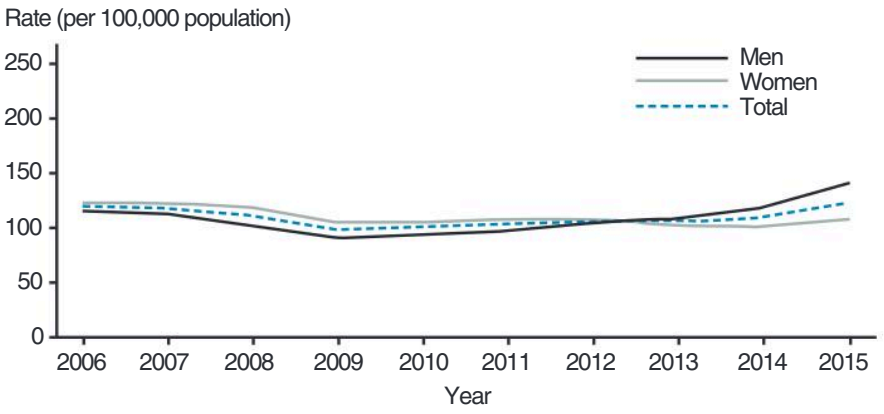


Fig. 2.16 Gonorrhea—rates of reported cases by sex, United States, 2006–15. (From Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2010*. Atlanta: US Department of Health and Human Services; 2016. https://www.cdc.gov/std/stats15/figures/13.htm. Accessed May 8, 2017.)

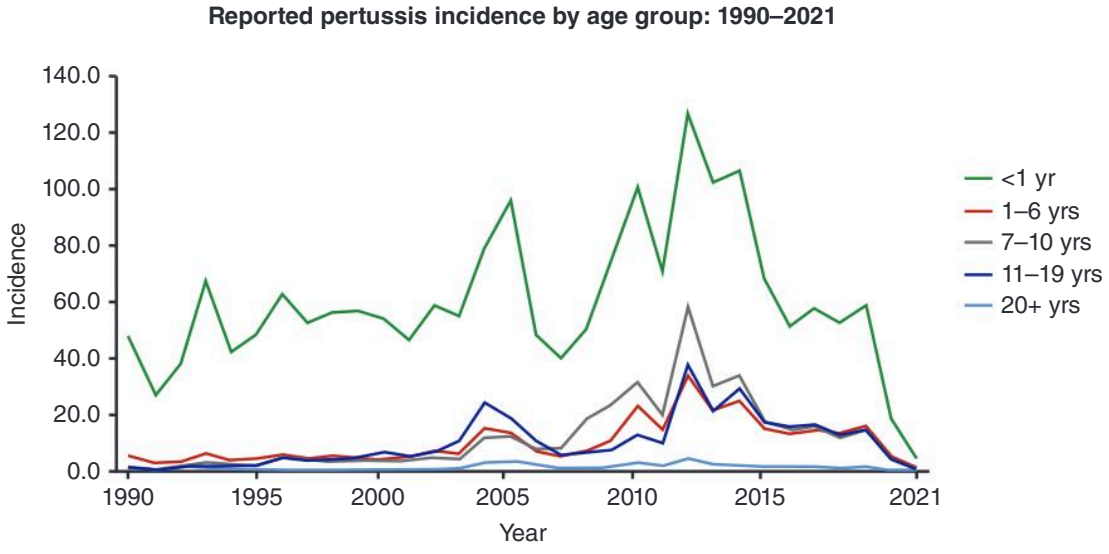


Fig. 2.17 Pertussis (whooping cough) incidence per 100,000 population by year and age group, United States, 1990–2021. (From Centers for Disease Control and Prevention. Pertussis (Whooping Cough): Surveillance and Reporting. https://www.cdc.gov/pertussis/surv-reporting.html. Accessed July 9, 2023.)

to be asymptomatic, the disease in women has probably been underreported. Rates had been leveling off in both men and women over the past few decades, but since 2013, higher rates of gonorrhea have been observed in men than in women. Such increases in rates among men could be either attributed to increased transmission or increased case ascertainment (e.g., through increased extragenital screening) among gay, bisexual, and other men who have sex with men.

Pertussis

The incidence of pertussis ("whooping cough") in the United States peaked in 2004 when the rate reached 8.9 cases per 100,000 population, more than twice that reported in 2003. In 1994, the rate was 1.8. The number of cases in 2004 was the highest reported since 1959. Although childhood pertussis vaccine coverage is high in the United States, pertussis continues to cause morbidity. Some of this increase may result from improved diagnostics as well as recognition and reporting of cases. As seen in Fig. 2.17, the lowest rates for pertussis in the United States were observed in 1991. Although incidence rates showed two more peaks in 2008 and 2009, they subsequently declined until 2016. Of note, infants aged less than 1 year, who are at the greatest risk for death, continue to have the highest reported rate of pertussis.

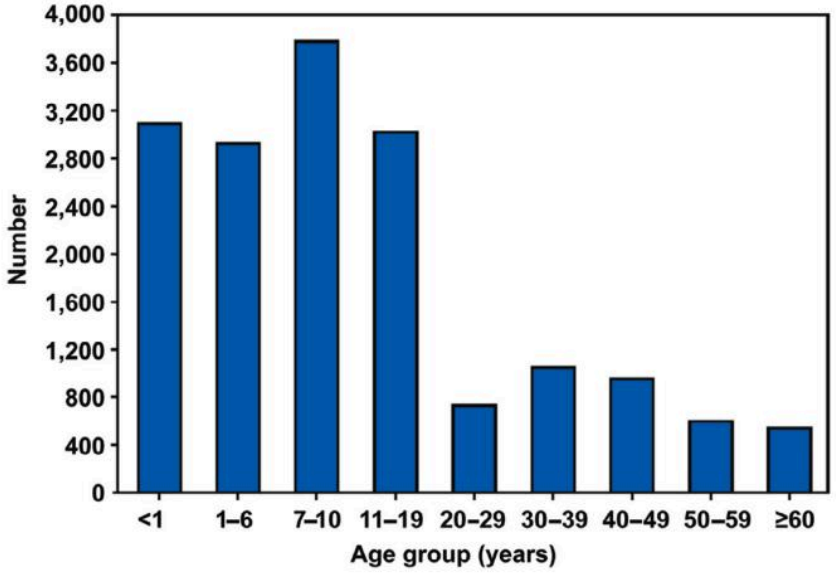


Fig. 2.18 Pertussis (whooping cough), reported numbers of cases by age group, United States, 2009. (From Centers for Disease Control and Prevention. Summary of notifiable diseases, United States, 2009. *Morb Mortal Wkly Rep*. 2011;58:1-100.)

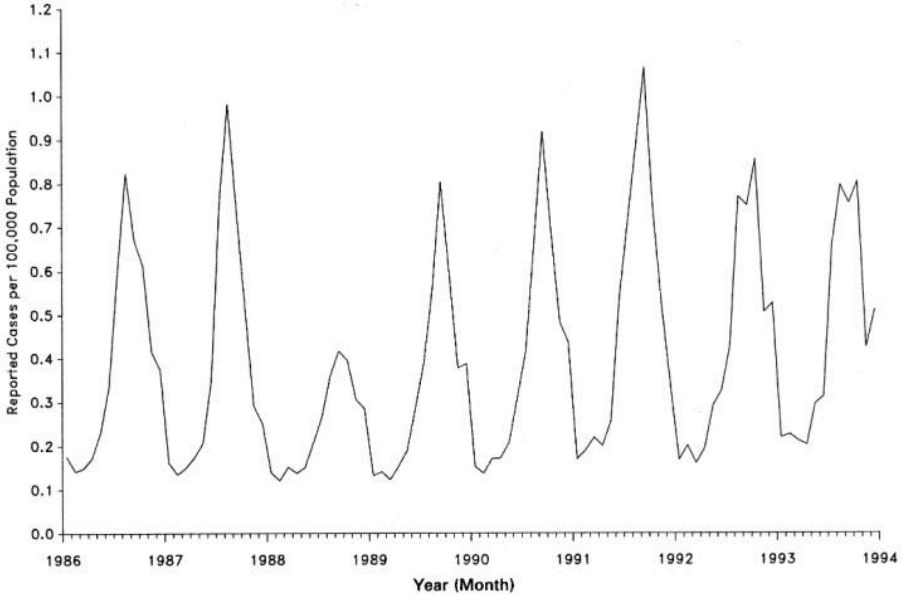


Fig. 2.19 Aseptic meningitis, reported cases per 100,000 population by month, United States, 1986–93. (From Centers for Disease Control and Prevention. Summary of notifiable diseases, United States, 1993. *Morb Mortal Wkly Rep*. 1994;42:22.)

Pertussis occurrence is clearly related to age (Fig. 2.18). Although the highest *rate* of pertussis was in infants less than 6 months of age (99 per 100,000 population), the *number* of reported cases was highest in children ages 11 to 19. Approximately half of reported pertussis cases in 2014 and 2015 occurred in 10- to 19-year-olds and in adults over the age of 20 years. Although the specific cause of this phenomenon is unknown, it could result from a waning of protection 5 to 10 years after pertussis immunization.

When?

Certain diseases occur with a certain periodicity. For example, aseptic meningitis peaks at consistent yearly rates (Fig. 2.19). Often, there is a seasonal pattern to the temporal variation. For example, diarrheal disease is