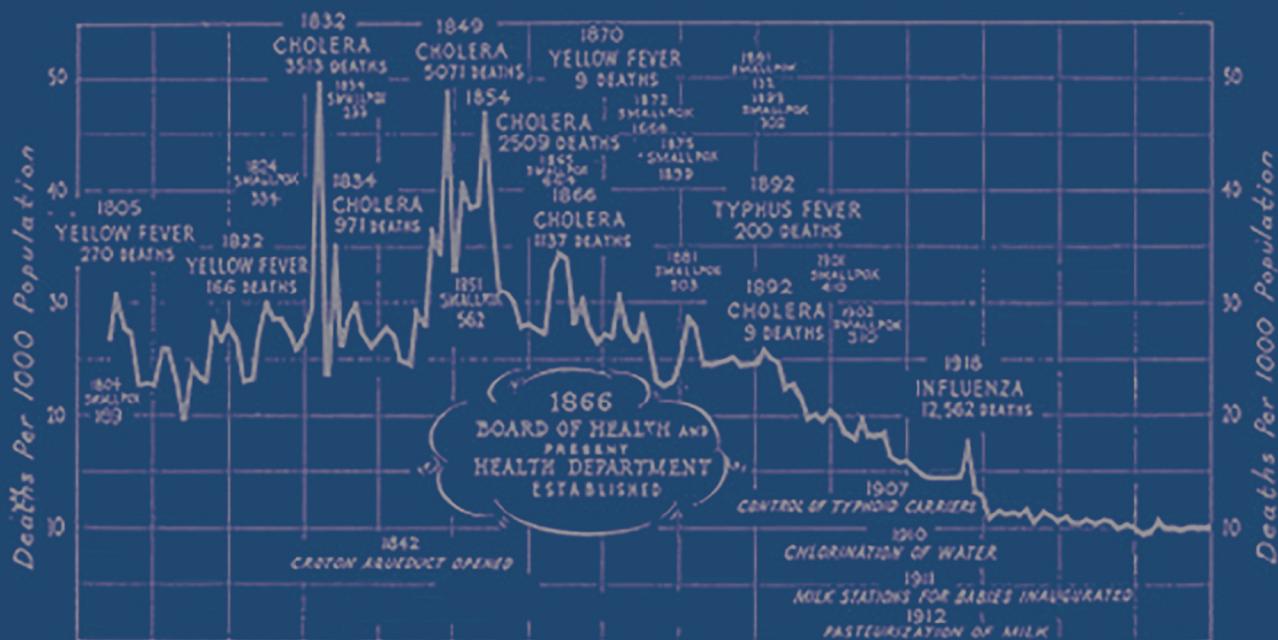


THIRD EDITION

PRINCIPLES OF BIOSTATISTICS



MARCELLO PAGANO

KIMBERLEE GAUVREAU

HEATHER MATTIE



CRC Press
Taylor & Francis Group

A CHAPMAN & HALL BOOK

Principles of Biostatistics



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Third Edition

Marcello Pagano

Kimberlee Gauvreau

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*This book is dedicated with love to
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Neil and Eliza,
Ali, Bud, Connie, Nanette, Steve, Katie and Buddy*



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Contents

Preface	xiii
1 Introduction	1
1.1 Why Study Biostatistics	1
1.2 Difficult Numbers	3
1.3 Overview of the Text	3
1.3.1 Part I: Chapters 2–4 Variability	4
1.3.2 Part II: Chapters 5–8 Probability	6
1.3.3 Part III: Chapters 9–22 Inference	6
1.3.4 Computing Resources	11
1.4 Review Exercises	12
I Variability	13
2 Descriptive Statistics	15
2.1 Types of Numerical Data	17
2.1.1 Nominal Data	17
2.1.2 Ordinal Data	17
2.1.3 Ranked Data	18
2.1.4 Discrete Data	18
2.1.5 Continuous Data	19
2.2 Tables	20
2.2.1 Frequency Distributions	20
2.2.2 Relative Frequency	22
2.3 Graphs	24
2.3.1 Bar Charts	24
2.3.2 Histograms	24
2.3.3 Frequency Polygons	26
2.3.4 Box Plots	29
2.3.5 Two-Way Scatter Plots	30
2.3.6 Line Graphs	31
2.4 Numerical Summary Measures	34
2.4.1 Mean	34
2.4.2 Median	36
2.4.3 Mode	37
2.4.4 Range	38
2.4.5 Interquartile Range	38
2.4.6 Variance and Standard Deviation	39
2.5 Empirical Rule	42
2.6 Further Applications	47
2.7 Review Exercises	56

3 Rates and Standardization	67
3.1 Rates	67
3.2 Adjusted Rates	70
3.2.1 Direct Standardization	72
3.2.2 Indirect Standardization	77
3.3 Further Applications	77
3.4 Review Exercises	84
4 Life Tables	89
4.1 Historical Development	90
4.2 Life Table as a Predictor of Longevity	95
4.3 Mean Survival	97
4.4 Median Survival	101
4.5 Further Applications	101
4.6 Review Exercises	106
II Probability	109
5 Probability	111
5.1 Operations on Events and Probability	111
5.2 Conditional Probability	115
5.3 Total Probability Rule	117
5.4 Relative Risk and Odds Ratio	121
5.5 Further Applications	126
5.6 Review Exercises	131
6 Screening and Diagnostic Tests	135
6.1 Sensitivity and Specificity	136
6.2 Bayes' Theorem	137
6.3 Likelihood Ratios	142
6.4 ROC Curves	145
6.5 Calculation of Prevalence	147
6.6 Varying Sensitivity	149
6.7 Further Applications	151
6.8 Review Exercises	155
7 Theoretical Probability Distributions	159
7.1 Probability Distributions	159
7.2 Binomial Distribution	161
7.3 Poisson Distribution	168
7.4 Normal Distribution	170
7.5 Further Applications	181
7.6 Review Exercises	186
8 Sampling Distribution of the Mean	191
8.1 Sampling Distributions	191
8.2 Central Limit Theorem	192
8.3 Applications of the Central Limit Theorem	193
8.4 Further Applications	198
8.5 Review Exercises	204

III Inference	207
9 Confidence Intervals	209
9.1 Two-Sided Confidence Intervals	209
9.2 One-Sided Confidence Intervals	213
9.3 Student's <i>t</i> Distribution	215
9.4 Further Applications	218
9.5 Review Exercises	222
10 Hypothesis Testing	227
10.1 General Concepts	227
10.2 Two-Sided Tests of Hypothesis	230
10.3 One-Sided Tests of Hypothesis	233
10.4 Types of Error	234
10.5 Power	238
10.6 Sample Size Estimation	241
10.7 Further Applications	243
10.8 Review Exercises	249
11 Comparison of Two Means	253
11.1 Paired Samples	254
11.2 Independent Samples	258
11.2.1 Equal Variances	259
11.2.2 Unequal Variances	263
11.3 Sample Size Estimation for Two Means	266
11.4 Further Applications	267
11.5 Review Exercises	274
12 Analysis of Variance	279
12.1 One-Way Analysis of Variance	279
12.1.1 The Problem	279
12.1.2 Sources of Variation	282
12.2 Multiple Comparisons Procedures	286
12.3 Further Applications	288
12.4 Review Exercises	293
13 Nonparametric Methods	297
13.1 Sign Test	297
13.2 Wilcoxon Signed-Rank Test	301
13.3 Wilcoxon Rank Sum Test	304
13.4 Kruskal-Wallis Test	307
13.5 Advantages and Disadvantages of Nonparametric Methods	311
13.6 Further Applications	311
13.7 Review Exercises	318
14 Inference on Proportions	323
14.1 Normal Approximation to the Binomial Distribution	324
14.2 Sampling Distribution of a Proportion	326
14.3 Confidence Intervals	327
14.4 Hypothesis Testing	329
14.5 Sample Size Estimation for One Proportion	330
14.6 Comparison of Two Proportions	332

14.7 Sample Size Estimation for Two Proportions	335
14.8 Further Applications	336
14.9 Review Exercises	345
15 Contingency Tables	351
15.1 Chi-Square Test	351
15.1.1 2×2 Tables	351
15.1.2 $r \times c$ Tables	356
15.2 McNemar's Test	358
15.3 Odds Ratio	360
15.4 Berkson's Fallacy	365
15.5 Further Applications	366
15.6 Review Exercises	373
16 Correlation	381
16.1 Two-Way Scatter Plot	381
16.2 Pearson Correlation Coefficient	382
16.3 Spearman Rank Correlation Coefficient	387
16.4 Further Applications	389
16.5 Review Exercises	395
17 Simple Linear Regression	399
17.1 Regression Concepts	399
17.2 The Model	402
17.2.1 Population Regression Line	402
17.2.2 Method of Least Squares	404
17.2.3 Inference for Regression Coefficients	408
17.2.4 Inference for Predicted Values	410
17.3 Evaluation of the Model	413
17.3.1 Coefficient of Determination	413
17.3.2 Residual Plots	414
17.3.3 Transformations	416
17.4 Further Applications	419
17.5 Review Exercises	425
18 Multiple Linear Regression	431
18.1 The Model	431
18.1.1 Least Squares Regression Equation	432
18.1.2 Inference for Regression Coefficients	434
18.1.3 Indicator Variables	435
18.1.4 Interaction Terms	436
18.2 Model Selection	438
18.3 Evaluation of the Model	440
18.4 Further Applications	442
18.5 Review Exercises	451
19 Logistic Regression	455
19.1 The Model	455
19.1.1 Logistic Function	457
19.1.2 Fitted Equation	458
19.2 Indicator Variables	460
19.3 Multiple Logistic Regression	464

19.4 Simpson's Paradox	466
19.5 Interaction Terms	467
19.6 Model Selection	468
19.7 Further Applications	469
19.8 Review Exercises	474
20 Survival Analysis	479
20.1 Life Table Method	481
20.2 Product-Limit Method	487
20.3 Log-Rank Test	491
20.4 Cox Proportional Hazards Model	495
20.5 Further Applications	496
20.6 Review Exercises	505
21 Sampling Theory	509
21.1 Sampling Designs	511
21.1.1 Simple Random Sampling	512
21.1.2 Systematic Sampling	514
21.1.3 Stratified Sampling	515
21.1.4 Cluster Sampling	519
21.1.5 Ratio Estimator	521
21.1.6 Two-Stage Cluster Sampling	523
21.1.7 Design Effect	526
21.1.8 Nonprobability Sampling	527
21.2 Sources of Bias	528
21.3 Further Applications	530
21.4 Review Exercises	535
22 Study Design	537
22.1 Randomized Studies	538
22.1.1 Control Groups	539
22.1.2 Randomization	539
22.1.3 Blinding	540
22.1.4 Intention to Treat	541
22.1.5 Crossover Trial	541
22.1.6 Equipoise	541
22.2 Observational Studies	542
22.2.1 Cross-Sectional Studies	542
22.2.2 Longitudinal Studies	543
22.2.3 Case-Control Studies	543
22.2.4 Cohort Studies	544
22.2.5 Consequences of Design Flaws	544
22.3 Big Data	544
22.4 Review Exercises	546
Bibliography	547
Glossary	569
Statistical Tables	583
Index	601



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Preface

This book was written for students of the health sciences and serves as an introduction to the study of biostatistics – the use of numbers and numerical techniques to extract information from data and facts, and to then use this information to communicate scientific results. However, just as one can lie with words, one can also lie with numbers. Indeed, numbers and lies have been linked for quite some time; there is even a book titled *How to Lie with Statistics*. This association may owe its origin – or its affirmation at the very least – to the British Prime Minister Benjamin Disraeli. Disraeli is credited by Mark Twain as having said, “There are three kinds of lies: lies, damned lies, and statistics.” One has only to observe any modern political campaign to be convinced of the abuse of statistics. But enough about lies; this book adopts the position of Professor Frederick Mosteller, who said, “It is easy to lie with statistics, but it is easier to lie without them.”

Background

Principles of Biostatistics is aimed at students in the biological and health sciences who wish to learn traditional research methods. The first edition was based on a required course for graduate students at the Harvard T.H. Chan School of Public Health, which is also attended by a large number of health professionals from the Harvard medical area. The course is as old as the school itself, which attests to its importance. It spans 16 weeks of lectures and laboratory sessions; the lab sessions reinforce the material covered in lectures and introduce the computer into the course. We have included a selection of lab materials – either additional examples, or a different perspective on the material covered in a chapter – in the sections called Further Applications. These sections are designed to provoke discussion, although they are sufficiently complete for an individual who is not using the book as a course text to benefit from reading them.

The book includes a range of biostatistical topics, the majority of which can be covered at some depth in one semester in an American university. However, there is enough material to allow the instructor some flexibility. For example, some instructors may choose to omit the sections covering the calculation of prevalence ([Section 6.5](#)) or the Poisson distribution ([Section 7.3](#)), or the chapter on analysis of variance ([Chapter 12](#)), if they consider these concepts to be less important than others.

Structure

Some say that statistics is the study of variability and uncertainty. We believe there is truth to this adage, and have used it as a guide to divide the book into three parts covering the basic principles of VIP: (1) variability, (2) inference, and (3) probability. For pedagogical purposes, inference and probability are covered in reverse order in the text. [Chapters 2 through 4](#) deal with the variability inherent in collections of numbers, and the ways in which to summarize, explore, and explain them. [Chapters 5 through 8](#) focus on probability, and serve as an introduction to the tools needed for the subsequent investigation of uncertainty. In [Chapter 8](#) we distinguish between populations and samples and begin to examine the variability introduced by sampling from a population, thus progressing to inference in the book’s remaining chapters. We think that this modular introduction to the quantification of uncertainty is justified by the success achieved by our students. Postponing

the slightly more difficult concepts until a solid foundation has been established makes it easier for the reader to comprehend and retain them.

Datasets and Examples

Throughout the text we have used data drawn from published studies to illustrate biostatistical concepts. Not only is real data more meaningful, it is usually more interesting as well. Of course, we do not wish to use examples in which the subject matter is too esoteric or too complex. To this end, we have been guided by the backgrounds and interests of our students – primarily topics in public health and clinical research – to choose examples that best demonstrate the concepts at hand.

There is some risk involved in using published data. We cannot guarantee that all of the examples are honest and that the data were properly collected; for this we must rely on the reputations of our sources. We do not belittle the importance of this consideration. The value of our inference depends critically on the worth of the data, and we strongly recommend that a good deal of effort be expended on evaluating its quality. We assume that this is understood by the reader.

In some cases we have used examples in which the population of the United States is broken down along racial lines. In reporting these official statistics we follow the lead of the government agencies that release them. We do not wish to rectify this racial categorization, since the observed differences may well be due to socioeconomic factors rather than the implied racial ones. One option would be to ignore these statistics; however, this would hide inequities which exist in our health system – inequities that need to be eliminated. We focus attention on the problem in the hope of stimulating interest in promoting solutions.

We have minimized the use of mathematical notation because of its well-deserved reputation of being the ultimate jargon. If used excessively, it can intimidate even the most ardent scholar. We do not wish to eliminate it entirely, however; it has been developed over the ages to be helpful in communicating results. In this third edition, mathematical notation and important formulas used in the text have also been included in summary boxes at the ends of relevant sections.

Computing

There is something about numbers – maybe a little magic – that makes them fun to study. The fun is in the conceptualization more than the calculations, however, and we are fortunate that we have the computer to do the drudge work. This allows students to concentrate on the concepts. In other words, the computer allows the instructor to teach the poetry of statistics and not the plumbing.

To take advantage of the computer, one needs a good statistical package. We use Stata, a product of the Stata Corporation in College Station, Texas, and also R, a software environment available for free download. Stata is user-friendly, accurate, powerful, reasonably priced, and works on a number of different platforms, including Windows, Unix, and Macintosh. R is available on an open-source license, and also works on a number of platforms. It is a versatile and efficient programming language. Other statistical packages are available, and this book can be supplemented by any one of them. We strongly recommend that some statistical package be used for calculations.

Some of the review exercises in the text require the use of a computer. The required datasets are available on the book's companion website at <https://github.com/Principles-of-Biostatistics/3rd-Edition>. There are also many exercises that do not require the computer. As always, active learning yields better results than passive observation. To this end, we cannot stress enough the importance of the review exercises, and urge the reader to attempt as many as time permits.

New to the Third Edition

The third edition continues in the spirit of the first edition, but has been updated to reflect some of the advances of the last 30 years. It includes revised and expanded discussions on many topics throughout the book. Major revisions include:

- The chapters on Data Presentation and Numerical Summary Measures from the second edition have been streamlined and combined into a single chapter titled Descriptive Statistics.
- The chapter on Life Tables has been rewritten, and detailed calculations for the life table have been moved into the Further Applications section.
- The material on Screening and Diagnostic Tests – formerly contained within the Probability chapter – has been given its own chapter. This new chapter includes sections on likelihood ratios and the concept of varying sensitivities.
- New sections on sample size calculations for two-sample tests on means and proportions, the Kruskal-Wallis test, and the Cox proportional hazards model have been added to existing chapters.
- Concepts previously covered in a chapter titled Multiple 2×2 Tables have now been moved into the Logistic Regression chapter.
- The chapter on Sampling Theory has been greatly expanded.
- A new chapter introducing the basic principles of Study Design has been added at the end of the text.
- Datasets used in the text and those needed for selected review exercises are now available on the book's companion website at <https://github.com/Principles-of-Biostatistics/3rd-Edition>.
- The companion website also contains the Stata and R code used to produce the computer output displayed in the text's Further Applications sections, as well as introductory material describing the use of both statistical packages.
- A glossary of definitions for important statistical terms has been added at the back of the book.
- As previously mentioned, mathematical notation and formulas used in the text have been included in summary boxes at the end of each section for ease of reference.
- Additional review exercises have been included in each chapter.

In addition to these changes in content, previously used data have been updated whenever possible to reflect more current public health information. As its name suggests, *Principles of Biostatistics* covers topics which are fundamental to an introduction to biostatistics. Of course we have had to limit the material presented, and some important topics have not been included. Decisions about what to exclude were difficult, especially as the field of biostatistics and data science continues to evolve. No small role in this evolution is played by the computer; the capacity of statistical software seems to increase limitlessly, providing new and exciting inferential tools. However, to truly appreciate these tools and to be able to utilize them properly requires a strong foundation in traditional statistical principles. Those laid out in this text are still essential and will be useful to the reader both today and in the future.

Acknowledgments

A debt of gratitude is owed to a number of people: former Harvard University President Derek Bok for providing the support which got the first edition of this book off the ground, Dr. Michael K. Martin for performing the calculations for the Statistical Tables section, John-Paul Pagano for assisting in the editing of the first edition, and the individuals who reviewed the manuscript. We thank the teaching assistants who have helped us teach our courses over the years and who have made many valuable suggestions. Probably the most deserving of thanks are our students, who have tolerated us as we learned how to best teach the material. We are still learning.

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Introduction

CONTENTS

1.1	Why Study Biostatistics	1
1.2	Difficult Numbers	3
1.3	Overview of the Text	3
1.3.1	Part I: Chapters 2–4 Variability	4
1.3.2	Part II: Chapters 5–8 Probability	6
1.3.3	Part III: Chapters 9–22 Inference	6
1.3.4	Computing Resources	11
1.4	Review Exercises	12

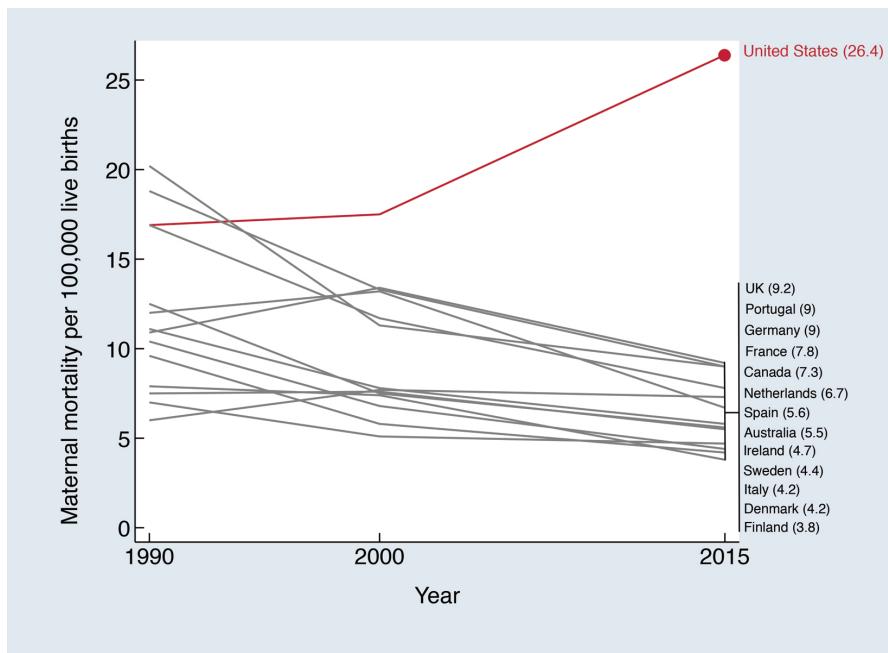
In 1903, H.G. Wells hypothesized that statistical thinking would one day be as necessary for good citizenship as the ability to read and write. Wells was correct, and today statistics play an important role in many decision-making processes. For example, before any new drug or medical device can be marketed legally in the United States, the United States Food and Drug Administration (FDA) requires that it be subjected to a *clinical trial*, an experimental study involving human subjects. The data from this study is compiled and analyzed to determine not only whether the drug is effective, but also if it is safe. How is this determined? As another example, the United States government's decisions regarding Social Security and public health programs rely in part on the longevity of the nation's population; the government must therefore be able to accurately predict the number of years each individual will live. How does it do this? If the government incorrectly forecasts human life expectancy, it could render itself insolvent and endanger the well-being of its citizens.

There are many other issues that must be addressed as well. Where should a government invest its resources if it wishes to reduce infant mortality? Should a mastectomy always be recommended to a patient with breast cancer? Should a child play football? What factors increase the risk that an individual will develop coronary heart disease? Will we be able to afford our health care system in the future? Does global warming impact the sea level? Our health? What effect would a particular change in policy have on longevity? To answer these questions and others, we rely on the methods of biostatistics.

1.1 Why Study Biostatistics

The study of *statistics* explores the collection, organization, analysis, and interpretation of numerical data. The concepts of statistics may be applied to a number of fields, including business, psychology, and agriculture. When focus is on the biological and health sciences, we use the term *biostatistics*.

Historically, statistics have been used to tell a story with numbers. Numbers often communicate ideas more succinctly than do words. For example, the World Health Organization (WHO) defines maternal mortality as “the death of a woman while pregnant or within 42 days of termination of

**FIGURE 1.1**

Maternal mortality per 100,000 live births, 1990–2015

pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes” [1]. Therefore, when presented with the graph in Figure 1.1 [2, 3], someone concerned with maternal mortality might react with alarm at the reported striking behavior of the United States and research the issue further.

How useful is the study of biostatistics? Biostatistics are certainly ubiquitous in the health sciences. The Centers for Disease Control and Prevention (CDC) reports that “During the 20th century, the health and life expectancy of persons residing in the United States improved dramatically. Since 1900, the average lifespan of persons in the United States has lengthened by greater than 30 years; 25 years of this gain are attributable to advances in public health” [4–6]. They go on to list what they consider to be ten great achievements:

- Vaccination
- Safer workplaces
- Healthier mothers and babies
- Fluoridation of drinking water
- Decline in deaths from coronary heart disease and stroke
- Motor vehicle safety
- Control of infectious diseases
- Safer and healthier foods
- Family planning
- Recognition of tobacco use as a health hazard

When one reads the recounting of these achievements in subsequent *Mortality and Morbidity Weekly Reports*, it is evident that biostatistics played an important role in every one of them.

Notwithstanding these societal successes, work still needs to be done. The future with its exabytes of data – known as *big data* – providing amounts of information which are orders of magnitude larger than was previously available is a new challenge. But if we are to progress responsibly, we cannot ignore the lessons of the past [7]. A case in point is our failure to control the number of deaths from guns that has led to a public health crisis in the United States. The statistic blared from a headline in

The New York Times in 2018 [8]: “NEARLY 40,000 PEOPLE DIED FROM GUNS IN U.S. LAST YEAR, HIGHEST IN 50 YEARS.” This crisis looks even worse when one considers what is happening with mass shootings in schools. The United States is experiencing a remarkable upward trend in the number of casualties involved. There have been more school shooting deaths in the first 18 years of the 21st century (66) than in the last 60 years of the 20th century (55). The same is true for injuries due to guns, with 260 and 81 in each of these two time periods, respectively [9]. A summary of this situation is made more pithy by the statistics.

1.2 Difficult Numbers

The numbers needed to tell a story are not always easy to come by – examples include attempts to investigate the volume of illicit human trafficking [10], or to measure the prevalence of female genital mutilation [11] – but are indispensable for communicating important ideas. The powerful use of statistics in this argument against continued restrictions on the drug mifepristone’s distribution is clear [12]:

Since its approval in 2000, more than 3.7 million women have used mifepristone to end an early pregnancy in the United States — it is approved for use up to 70 days into a pregnancy. Nearly two decades of data on its use and effects on patients provide significant new insights into its safety and efficacy. Mifepristone is more than 97% effective. Most adverse effects are mild, such as cramping or abdominal pain, and the rate of severe adverse events is very low: such events occur in less than 0.5% of patients, according to the FDA. Many drugs marketed in the United States have higher adverse event rates and are not subject to restricted distribution.

In this example, the numbers provide a concise summary of the situation being studied. They, of course, must be both accurate and precise if we are to trust any conclusions based on them.

The examples described deal with complex situations, yet the numbers convey essential information. A word of caution: we must remain realistic in our expectations of what statistics can achieve. No matter how powerful it is, no statistic will convince everyone that a given conclusion is true. The data on gun deaths in the United States mentioned above are often brushed away with some variant of the aphorism, “Guns don’t kill people, people do.” This should not come as a surprise. After all, there are still deniers of global warming, people who believe that the vaccine for measles, mumps, and rubella causes autism, and members in the Flat Earth Society, whose website states: “This website is dedicated to unravelling the true mysteries of the universe and demonstrating that the earth is flat and that Round Earth doctrine is little more than an elaborate hoax” [13].

1.3 Overview of the Text

The aim of a study using biostatistics is to analyze and present data in a transparent, interpretable, and coherent manner to effectively communicate results and to help lead policy makers to the best informed decisions. This text book, as its title states, covers the principles of biostatistics. The 21 chapters beyond this one can be arranged into three parts to cover the tenets of biostatistics: (1) variability, (2) inference, and (3) probability. We list them in this order so students can easily remember the acronym VIP. For pedagogical reasons, however, we present them in a different order:

Coronavirus cases per 10,000 people

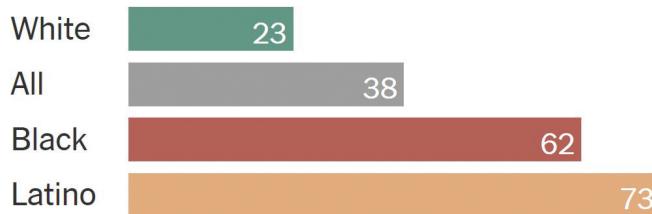


FIGURE 1.2

Racial breakdown of COVID-19 cases in the United States through May 28, 2020

(1) [Chapters 2–4](#) discuss variability, (2) [Chapters 5–8](#) cover probability, and (3) [Chapters 9–22](#) cover inference.

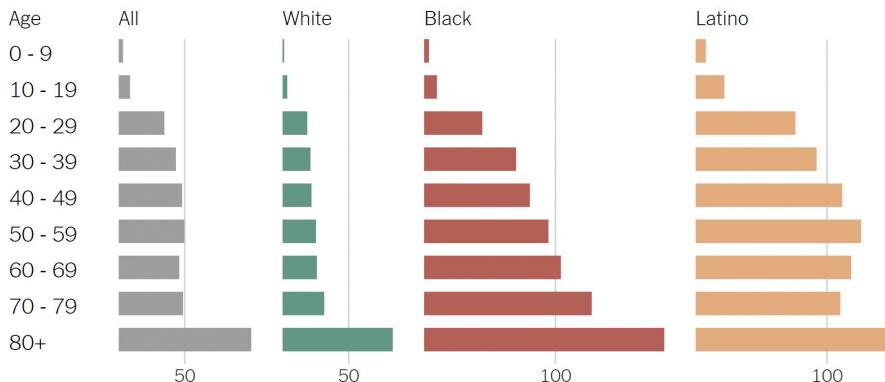
1.3.1 Part I: Chapters 2–4 Variability

If we wish to study the effects of a new diet, we might place a group of individuals on that diet and measure changes in their body mass over time. Similarly, if we want to investigate the success of an innovative therapy for treating pancreatic cancer, we might record the lengths of time that patients treated with this therapy survive beyond their initial diagnosis. These numbers, however, can display a great deal of variability from one person to another. They are generally not very informative until we begin combining them in some way. Descriptive statistics, the topic of [Chapter 2](#), are methods for organizing and summarizing a set of measurements. They help us to better understand the attributes of a group or population. For instance, to support the premise that there was racial inequity in who was afflicted by the coronavirus, reporters from *The New York Times* collected data and displayed it not only in a table, but also as a graph similar to [Figure 1.2](#) [14]. To dig deeper into their analysis and show the impact by age group, they also included [Figure 1.3](#) [14]. This example demonstrates the power of a picture to tell a story. The graphical capabilities of computers make this type of summarization feasible even for the most modest analyses, and use of both tables and graphs to summarize information enables scientists and policy makers to formulate hypotheses that then require further investigation.

By definition, a summary captures only a particular aspect of the data being studied; consequently, it is important to have an idea of how well the summary represents the set of measurements as a whole. For example, we might wish to know how long HIV/AIDS patients survive after diagnosis with one of the opportunistic infections that characterize the disease. If we calculate an average survival time, is this average representative of all patients? Furthermore, how useful is it for planning future health service needs? In addition to tables and graphs, [Chapter 2](#) examines numerical summary measures that help answer questions such as these. The chapter includes an introduction to the mean and standard deviation; the former tells us where the measurements are centered, and the latter how dispersed they are. The chapter ends with the splendid empirical rule, which quantifies the metaphor “the apple does not fall far from the tree.”

Measurements that take on only two distinct values require special attention. In the health sciences, one of the most common examples of this type of data is the categorization of being alive or dead. If we denote survival by 0 and death by 1, we are able to classify each member of a group of individuals using these numbers and then average the results. In this way, we can summarize the mortality associated with the group. [Chapter 3](#) deals exclusively with measurements

Coronavirus cases per 10,000 people, by age and race



Source: Centers for Disease Control and Prevention | Note: Data is through May 28.

FIGURE 1.3

Racial breakdown of COVID-19 cases in the United States in 2020, by age

that assume only two values. The notion of dividing a group into smaller subgroups or classes based on a characteristic such as age or sex is also introduced. Grouping individuals into smaller, more homogeneous subgroups decreases variability, thus allowing better prognosis. For example, it might make sense to determine the mortality of females separately from that of males, or the mortality of 20- to 29-year-olds separately from 80- to 89-year-olds. [Chapter 3](#) also investigates techniques that allow us to make valid comparisons among populations whose compositions may differ substantially.

[Chapter 4](#) introduces the classical life table, one of the most important numerical summary techniques available in the health sciences. Life tables are used by public health professionals to characterize the well-being of a population, and by insurance companies to predict how long individuals will live. In this chapter, the study of mortality begun in [Chapter 3](#) is extended to incorporate the actual time to death for each individual, resulting in a more refined analysis.

Together, [Chapters 2](#) through [4](#) demonstrate that the extraction of information from a collection of measurements is not precluded by the variability among those measurements. Despite their variability, the data often exhibit a certain regularity as well. For example, here are the birth rates in the United States among women 15–19 years of age over the 5-year time span shown [15]:

Year :	2011	2012	2013	2014	2015
Birth rate per 1000 :	31.3	29.4	26.5	24.2	22.3

Are the numbers showing a natural variability around a constant rate over time – think of how many mistakes can go into the reporting of such numbers – or is this indicative of a real downward trend? This question deserves better than a simple choice between these two options. To answer it properly, we need to apply the principles of probability and inference, the subjects covered in the next two sections of the text.

1.3.2 Part II: Chapters 5–8 Probability

Probability theory resides within what is known as an axiomatic system; we start with some basic truths (axioms), and then build up a logical system around them. In its purest form, this theoretical system has no practical value. Its practical importance comes from knowing how to use the theory to yield useful approximations. An analogy can be drawn with geometry, a subject that most students are exposed to relatively early in their schooling. Although it is impossible for an ideal straight line to exist other than in our imaginations, that has not stopped us from constructing some wonderful buildings, based on geometric calculations; including some that have lasted thousands of years. The same is true of probability theory. Although it is not practical in its pure form, its basic principles – which we investigate in [Chapter 5](#) – can be applied to provide a means of quantifying uncertainty.

An important application of probability theory arises in medical screening and diagnostic testing, as we see in [Chapter 6](#). Uncertainty is present because, despite some manufacturers' claims, no biological test is perfect. This leads to complicated findings, which are sometimes unintuitive, even in the simple situation where the test is diagnosing the presence or absence of a medical condition. Before performing the test, we consider each of four possible classifications: the test result is correct or not, and the person being tested has the condition or not. The relationship between the results of the test and the truth gives rise to important practical questions. For instance, can we conclude that every blood sample that tests positive for HIV actually harbors the virus? All the units in the Red Cross blood supply have tested negative for HIV; does this mean that there are no contaminated samples? If there are contaminated samples, how many might there be? To address questions such as these, we study the average or long-term behavior of diagnostic tests by using probability theory.

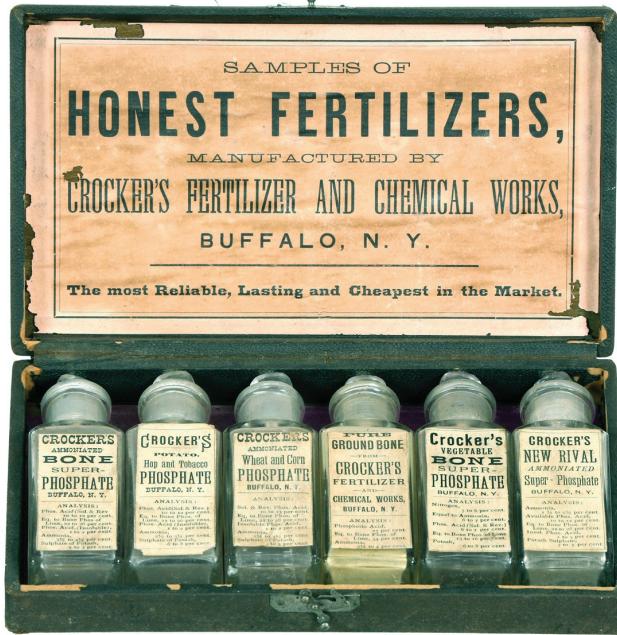
[Chapters 7 and 8](#) extend probability theory and introduce some common probability distributions used to describe the variability in a set of measurements. These mathematical models are useful as a basis for the inferential methods covered in the remainder of the text.

1.3.3 Part III: Chapters 9–22 Inference

The *Cambridge Dictionary* defines *inference* as a guess that is made or an opinion that is formed based on the information available. The paradigm we use in this text is that the inference we make about a population is based on a sample of observations selected from that much larger population. On the basis of the sample, we draw conclusions about the entire population, including the part of the population we did not measure – those not in the sample. Humans are much more similar to each other than dissimilar, and we capitalize on this fact to add credibility to our inference. However, knowing how the sample is chosen and whom the sample represents are also of critical importance for making inference.

An analogy can be made with the way in which traveling salesmen in the late 19th and early 20th centuries in the United States were able to sell their goods to potential customers. Rather than carry all the goods to be sold – including big items such as stoves – they would transport miniature models of the products they were selling; see [Figure 1.4](#) for an example. These replicas were very carefully crafted, so as to convey an honest likeness, albeit a much smaller version of the sale item [16]. Although these are also called samples, this is where the analogy ceases to be useful; to make realistic models, the manufacturers had the real item as a guide. When we sample in biostatistics, it is because we do not know what the measurements look like for the entire target population.

Suppose we want to know whether a new drug is effective in lowering high blood pressure. Since the population of all people in the world who have high blood pressure is very large, it is implausible to think we would have either the time or the resources necessary to locate and examine each and every person with this condition who might be a candidate to use the drug. Out of necessity, we must rely on a sample of people drawn from the population. The limits to our subsequent inference – which are always there – are determined by both the population that we sample, and by how well the sample represents that population.

**FIGURE 1.4**

Boxed salesman's sample set of glass bottles, containing samples from the Crocker company (Buffalo, New York) (photo courtesy of Judy Weaver Gonyea) [16]

The ability to generalize results from a sample to a population is the bedrock of empirical research, and a central issue in this book. One requirement for credible inference is that it be based on a representative sample. In any particular study, do we truly have a representative sample? If we answer yes, this leads to a logical conundrum. To truly judge that we have a representative sample we need to know the entire population. And if we know the entire population, why then focus only on a sample? If we do not have the ability to study an entire population, the best solution available is to utilize a simple random sample of the population. This means, amongst other things, that everyone in the population has an equal chance of being selected into the sample. It ensures us that, *on average*, we have a representative sample. A pivotal side benefit of a simple random sample is that it also provides an estimate of the possible inaccuracy of our inference.

It can often be difficult to obtain a simple random sample. The consequences of mistakenly thinking that a sample is representative when in fact it is not lead to invalid inferences. A case in point is provided by the behavioral sciences, where empirical results are often derived from individuals sampled from western, educated, industrialized, rich, and democratic (WEIRD) societies. An example of this is the undergraduate students who make a few extra dollars by volunteering to be a subject for an on-campus study. Since most of these studies are done in the United States, we can see the problem. Clearly the results will reflect the pool from which the subjects came. Use of the label WEIRD implies a certain contempt for a large number of published findings attacked in an article by Henrich and colleagues [17]. They investigate results in the domains of visual perception, fairness, cooperation, spatial reasoning, categorization and inferential induction, moral reasoning, reasoning styles, self-concepts and related motivations, and the heritability of IQ. They conclude that “members of WEIRD societies, including young children, are among the least representative populations one could find for generalizing about humans.” Yet the researchers who published the original results presumably believed that their samples were random and representative.

We have repeated this mistake in the bio-medical sciences, where the consequences can be even more severe. For example, we do not perform as many clinical trials on children as on adults [18]. Trials of adults, even randomized clinical trials, are not representative of children. Children are not small adults who simply require a modification in dosage. Some conditions – such as prematurity and many of its sequelae – occur only in infants and children [19]. Certain genetic conditions such as phenylketonuria (PKU) will, if untreated, lead to severe disability or even death in childhood. The diagnosis, prevention, and treatment of these conditions cannot be adequately investigated without studying children. Other conditions such as influenza and certain cancers and forms of arthritis also occur in both adults and children, but their pathophysiology, severity, course, and response to treatment may be quite different for infants, children, and adolescents. Treatments that are safe and effective for adults may be dangerous or ineffective for children.

There are many more examples where certain groups have been largely ignored by researchers. The lack of trials in women [20] and people of color led Congress, in 1993, to pass the National Institutes of Health Revitalization Act, which requires the agency to include more people from these groups in their research studies. Unfortunately, success in the implementation of this law has been slow [21]. The headline in *Scientific American* on September 1, 2018 – 25 years after the Act was passed – was CLINICAL TRIALS HAVE FAR TOO LITTLE RACIAL AND ETHNIC DIVERSITY; IT'S UNETHICAL AND RISKY TO IGNORE RACIAL AND ETHNIC MINORITIES [22].

This problem extends beyond clinical trials. The 21st century has seen the mapping of the human genome. Genome wide association studies (GWAS) have identified thousands of genetic variants identified with human traits and diseases. This exciting source of information is unfortunately restricted, so inference is constrained or biased. A 2009 study showed that 96% of participants in GWAS studies were of European descent [23]. Seven years later this had decreased to 80%, largely due to studies carried out in China and Japan; the Asian content has increased, but the representation of other groups has not. Since GWAS studies are the basis for *precision medicine*, this has raised the fear that precision medicine will exacerbate racial health disparities [24]. This, of course, is a general trait of artificial intelligence systems: they reflect the information that goes into them.

As an example of the value of inference, we can consider a group of investigators who were interested in evaluating whether, at the time of their study, there was a difference in how analgesics were administered to male versus female patients with acute abdominal pain. It would be impossible to investigate this issue by observing every person in the world with acute abdominal pain, so they designed a study of a smaller group of individuals with this ailment so they could, on the basis of the sample, infer what was happening in the population as a whole. How far their inference should reach is not our focus right now, but it is important to take notice of what they say. Here is a copy of the abstract from the published article [25]:

OBJECTIVES: Oligoanalgesia for acute abdominal pain historically has been attributed to the provider's fear of masking serious underlying pathology. The authors assessed whether a gender disparity exists in the administration of analgesia for acute abdominal pain.

METHODS: This was a prospective cohort study of consecutive nonpregnant adults with acute nontraumatic abdominal pain of less than 72 hours duration who presented to an urban emergency department (ED) from April 5, 2004, to January 4, 2005. The main outcome measures were analgesia administration and time to analgesic treatment. Standard comparative statistics were used.

RESULTS: Of the 981 patients enrolled (mean age \pm standard deviation [SD] 41 ± 17 years; 65% female), 62% received any analgesic treatment. Men and women had similar mean pain scores, but women were less likely to receive any analgesia (60% vs. 67%, difference 7%, 95% confidence interval (CI) = 1.1% to 13.6%) and less likely to receive opiates (45% vs. 56%, difference 11%, 95% CI = 4.1% to 17.1%). These differences persisted when gender-specific diagnoses were excluded (47% vs. 56%, difference 9%, 95% CI = 2.5% to 16.2%). After controlling for age, race, triage class, and pain score, women were still 13% to 25%

less likely than men to receive opioid analgesia. There was no gender difference in the receipt of nonopioid analgesia. Women waited longer to receive their analgesia (median time 65 minutes vs. 49 minutes, difference 16 minutes, 95% CI = 3.5 to 33 minutes).

CONCLUSIONS: Gender bias is a possible explanation for oligoanalgesia in women who present to the ED with acute abdominal pain. Standardized protocols for analgesic administration may ameliorate this discrepancy.

This is a fairly typical abstract in the health sciences literature – it reports on a clinical study and uses statistics to describe the findings – so we look at it more closely. First consider the objectives of the study. We are told that the goal is to discover whether there is a gender disparity in the administration of drugs. This is not whether there was a difference in administering the drugs between genders in this particular study – that question is easy to answer – but rather a more ambitious finding; namely, is there something in this study that allows us to generalize the findings to a broader population?

The abstract goes on to describe the methods utilized in the study, and then its results. We first learn that the researchers studied a group of 981 patients. To allow the reader to get an understanding of who these 981 patients are, they provide some descriptive statistics about the patients' ages and genders. This is done to lay the groundwork for generalizing the results of the study to individuals not included in the study sample.

The investigators then start generalizing their results. We are told that even though men and women suffered similar amounts of pain, women were less likely – 7% less likely – to receive any analgesia. This difference of 7% is clearly study specific. Had they chosen fewer than 981 patients or more, or even a different group of 981 patients, they likely would have observed a difference other than 7%. How to quantify this potential variability from sample to sample – even though we have observed only a single sample – and how to accommodate it when making inference, is answered by the most useful and effective result in the book. It is an application of the theory covered in [Chapter 8](#), and is known as the central limit theorem.

An application of the central limit theorem allows the study investigators to construct a 95% confidence interval for the difference in proportions, 1.1% to 13.6%. One way to interpret this interval is to appeal to a thought experiment and repetition: If we were to sample repeatedly from the underlying population, each sample might result in a difference other than 7%, and a confidence interval other than 1.1% to 13.6%. However, 95% of these intervals from repeated sampling will include the *true* population difference between the genders, whatever its value. The interpretations for all the other confidence intervals in the abstract are similar. More general applications of confidence intervals are introduced in [Chapter 9](#), and examples appear throughout the text.

For a study to be of general interest and usefulness, we must be able to extrapolate its findings to a larger population. By generalizing in this manner, however, we inevitably introduce uncertainty. There are various ways to measure and convey this uncertainty, and we cover two such inferential methods in this book. One is to use confidence intervals, as we just saw in the abstract, and the other is to use hypothesis testing. The latter is introduced in [Chapter 10](#). The two methods are consistent with each other, and will lead to the same action following a study. There are some questions, however, that are best answered in the hypothesis testing framework.

As an example, consider the way we monitor the water supply for lead contamination [[26](#)]. In 1974, the United States Congress passed the Safe Drinking Water Act, and its enforcement is a responsibility of the Environmental Protection Agency (EPA). The EPA determines the level of contaminants in drinking water at which no adverse health effects are likely to occur, with an adequate margin of safety. This level for lead is zero, and untenable. As a result, the EPA established a treatment technique, an enforceable procedure which water systems must follow to ensure control of a contaminant. The treatment technique regulation for lead – referred to as the Lead and Copper Rule [[27](#)] – requires water systems to control the corrosivity of water. The regulation stipulates that to determine whether a system is safe, health regulators must sample taps in the system that are

more likely to have plumbing materials containing lead. The number of taps sampled depends on the size of the system served. To accommodate aberrant local conditions, if 10% or fewer of the sampled taps have no more than 15 parts per billion (ppb) of lead, the system is considered safe. If not, additional actions by the water authority are required. We can phrase this monitoring procedure in a hypothesis testing framework: We wish to test the hypothesis that the water has 15 ppb or fewer of lead. The action we take depends on whether we reject this hypothesis, or not. According to the Lead and Copper Rule, the decision depends on the measured tap water samples. If more than 10% of the water samples have more than 15 ppb, we reject the hypothesis and take corrective action.

Just as with diagnostic testing in [Chapter 6](#), we have the potential to make the wrong decision when conducting a hypothesis test. The chance of such an error is influenced by the way in which the samples are chosen, how many samples we take, and the 10% cutoff rule. In 2015, the city of Flint, Michigan, took water samples in order to check the level of lead in the water [28]. According to the Lead and Copper Rule, they were supposed to take 100 samples from houses most likely to have a lead problem. They did not. First, they took only 71 samples; second, they chose the 71 in what seemed like a random fashion. Setting aside these contraventions, they found that 8 of the 71 samples had more than 15 ppb. This is more than 10% of the samples, and thus they were required to alert the public and take corrective action. Instead, the State of Michigan forced Flint to drop two of the water samples, both with more than 15 ppb of lead. This meant that there were only 69 samples, and 6 had more than 15 ppb of lead. Thus fewer than 10% crossed the threshold, and the authorities felt free to tell the residents of Flint that their water was fine. This is yet another example of ignoring the message produced by the scientific method and having catastrophe follow [29]. It seems like the lead problem is repeating itself, only this time in Newark, New Jersey [30].

In [Chapter 10](#) we apply hypothesis testing techniques to statements about the mean of a single population, and in [Chapter 11](#) extend these techniques to the comparison of two population means. They are further generalized to the comparison of three or more means in [Chapter 12](#). [Chapter 13](#) continues the development of hypothesis testing concepts, but introduces techniques that allow the relaxation of some of the assumptions necessary to carry out the tests. [Chapters 14 and 15](#) develop inferential methods that can be applied to enumerated data or counts – such as the numbers of cases of sudden infant death syndrome among children put to sleep in various positions – rather than continuous measurements.

Inference can also be used to explore the relationships among a number of different attributes, with the underlying motivation being to reduce variability. If a full-term infant whose gestational age is 39 weeks is born weighing 4 kilograms, or 8.8 pounds, no one would be surprised. If the infant's gestational age is only 22 weeks, however, then their weight would be cause for alarm. Why? We know that birth weight tends to increase with gestational age, and, although it is extremely rare to find a baby weighing 4 kilograms at 22 weeks, it is not uncommon at 39 weeks. There is sufficient variability in birth weights to not be surprised to hear that an infant weighs 4 kilograms at birth, but when the gestational age of the child is known, there is much less variability among infants of a particular gestational age, and 4 kilograms may seem out of place. In other words, our measurements have a more precise interpretation the more information we have about the measurement.

The study of the extent to which two factors are related is known as correlation analysis; this is the topic of [Chapter 16](#). If we wish to predict the outcome of one factor based on the value of another, then regression is the appropriate technique. Simple linear regression is investigated in [Chapter 17](#), and is extended to the multiple regression setting – where two or more factors are used to predict a single outcome – in [Chapter 18](#). If the outcome of interest can take on only two possible values, such as alive or dead, then an alternative technique must be applied; logistic regression is explored in [Chapter 19](#).

In [Chapter 20](#), the inferential methods appropriate for life tables are introduced. These techniques enable us to draw conclusions about the mortality of a population based on the experience of a sample of individuals drawn from the population. This is common in clinical trials, especially in randomized

clinical trials, when the purpose of the trial is to study whether a patient's survival has been prolonged by a treatment [31].

Chapter 21 is devoted to surveys and inference in finite populations. These techniques are very popular around election time in democracies, but also find many uses in public health. For example, the United States Census Bureau supplements the decennial census with an annual survey called the American Community Survey; its purpose is to help “local officials, community leaders, and businesses understand the changes taking in their communities. It is the premier source for detailed population and housing information about our nation” [32]. In 2017, 2,145,639 households were interviewed. Once again, the mainstay that enables us to make credible inference about the entire United States population, 325.7 million people in 2017, is the *simple random sample*. We take that as our starting point, and build on it with more refined designs. Practical examples are given by the National Centers for Health Statistics within the CDC [33].

Once again it would be helpful if we could control variability and lessen its effect. Some survey designs help in this regard. For example, if we can divide a population into strata where we know the size of each stratum, we can take advantage of that extra information – the size of the strata – to estimate the population characteristics more accurately via *stratified sampling*. If on the other hand we wish to lower the cost of the survey, we can turn to *cluster sampling*. Of course, we can combine these ideas and utilize both in a single survey. These design considerations and some of the issues raised are addressed in this chapter.

The last chapter, Chapter 22, could have been the first. Even though it is foundational, one needs the material developed in the rest of the book to appreciate its content. It is here that we bolster the belief that it is not just the numbers that count, but what they represent, and how they are obtained. This was made quite clear during the COVID-19 pandemic. The proper monitoring of a viral epidemic and its course requires an enumeration of people infected by the virus. This, unfortunately, did not happen. Miscounting of COVID-19 cases occurred across the world [34], including the United States [35,36]. One cannot help but think that this disinformation contributed to the resultant damage from the pandemic.

Chapter 22 explores how best to design studies to take advantage of the methods described in this book. It also should whet your appetite to study biostatistics further, as the story gets even more fascinating. To quote what George Udny Yule wrote almost a century ago [37]:

When his work takes an investigator out of the field of the nearly perfect experiments, in which the influence of disturbing causes is practically negligible, into the field of imperfect experiment (or *a fortiori* of pure observation) where the influence of disturbing causes is important, the first step necessary for him is to get out of the habit of thinking in terms of the single observation and to think in terms of the average. Some seem never to get beyond this stage. But the next state is even more important, *viz.*, to get out of the habit of thinking in terms of the average, and think in terms of the frequency distribution. Unless and until he does this, his conclusions will always be liable to fallacy.

1.3.4 Computing Resources

In addition to Stata output, R output is presented for all examples in the Further Applications sections of each chapter. In addition, all Stata and R code is available online, and can be accessed at <https://github.com/Principles-of-Biostatistics/3rd-Edition>.

1.4 Review Exercises

1. Design a study aimed at investigating an issue you believe might influence the health of the world. Briefly describe the data you will require, how you will obtain them, how you intend to analyze the data, and the method you will use to present your results. Keep this study design and reread it after you have completed the text.
2. Suppose it is stated that in a given year, 512 million people around the world were malnourished, up from 460 million just five years prior [38].
 - (a) Suppose that you sympathize with the point being made. Justify the use of these numbers.
 - (b) Are you sure that the numbers are correct? Do you think it is possible that 513 million people were malnourished during the year in question rather than 512 million?
3. In addition to stating that “the Chinese have eaten pasta since 1100 b.c.,” the label on a box of pasta shells claims that “Americans eat 11 pounds of pasta per year,” whereas “Italians eat 60 pounds per year.” Do you believe that these statistics are accurate? Would you use these numbers as the basis for a nutritional study?

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